Third Inter-American Congress of Cardiology
Chicago, June 13-17, 1948

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VOL. 35 MARCH, 1948 No. 3

AMERICAN HEART JOURNAL

For the Study of the CIRCULATION

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Published Monthly Under the Editorial Direction of The American Heart Association

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Contents on Inside Cover

American Heart Journal

CONTENTS FOR MARCH, 1948

Original Communications

The Effect of Occlusive Arterial Diseases of the Extremities on the Blood Supply of Nerves. Experimental and Clinical Studies on the Role of the Vasa Nervorum. Joseph Thomas Roberts, M.D., Ph.D., Little Rock, Ark., with the Technical Assistance of W. H. Jarvis, R. S. Browne, F. D. Spencer, Jr., Julian Key, J. A. Rivas, and D. Brandt 369

Experience With Three Vascular Fragility Tests in Hypertension. John Schweppe, M.D., Howard A. Lindberg, M.D., and M. Herbert Barker, M.D., Chicago, Ill. 393

Night Cramps in Human Extremities. Harold K. Moss, M.D., and Louis G. Herrmann, M.D., Cincinnati, Ohio 403

The Relation Between Arterial Pressure and Blood Flow in the Foot. P. Scheinberg, M.D., E. W. Dennis, R. L. Robertson, M.D., and E. A. Stead, Jr., M.D., Atlanta, Ga. 409

Electrocardiogram in Chronic Cor Pulmonale. Rudolf Zuckermann, M.D., Enrique Cabrera C., M.D., Bernardo L. Fishleder, M.D., and Demetrio Sodi-Pallares, M.D., Mexico, D.F., Mexico 421

The Familial Incidence of Rheumatic Fever. I. A Discussion of the Relationship Between a Positive Family History and the Development of Rheumatic Fever in Individuals of Military Age. George C. Griffith, M.D., and Frederick J. Moore, M.D., Pasadena, Calif., Sylvester McGinn, M.D., Boston, Mass., and Richard S. Cosby, M.D., Pasadena, Calif. 438

The Familial Incidence of Rheumatic Fever. II. A Statistical Study of the Familial and Personal History of Rheumatic Fever. George C. Griffith, M.D., and Frederick J. Moore, M.D., Pasadena, Calif., Sylvester McGinn, M.D., Boston, Mass., and Richard S. Cosby, M.D., Pasadena, Calif. 444

Different Mechanisms of Fusion Beats. M. R. Malinow, M.D., and R. Langendorf, M.D., Chicago, Ill. 448

Glossopharyngeal Neuralgia: A Cause of Cardiac Arrest. Bronson S. Ray, M.D., and Harold J. Stewart, M.D., New York, N. Y. 458

The Diminished Efficiency and Altered Dynamics of Respiration in Experimental Pulmonary Congestion. Howard E. Heyer, M.D., James Holman, M.D., and George T. Shires, Dallas, Texas 463

Prolongation of the Q-T Interval in the Electrocardiogram Occurring as a Temporary Functional Disturbance in Healthy Persons. Orville Horwitz, M.D., Philadelphia, Pa., and Captain Ashton Graybiel, Medical Corps, United States Navy 480

Clinical Reports

Death Following Coronary Thrombosis in a Young Woman Nineteen Years of Age. Commander Willis F. Evans, Medical Corps, United States Naval Reserve (Inactive), and Captain Ashton Graybiel, Medical Corps, United States Navy 485

Pericardial Effusion Due to Hemolytic Streptococcus Following an Acute Upper Respiratory Infection; Associated Pleural Effusions. Seymour H. Rinzler, M.D., and Sidney Leibowitz, M.D., New York, N. Y. 490

Interatrial Septal Defect Associated With Syphilitic Aortic Insufficiency. Morris Lipson, M.D., Los Angeles, Calif. 497

Abstracts and Reviews

Selected Abstracts 506

American Heart Association, Inc. 527

Vol. 35, No. 3, March, 1948, American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Avenue, St. Louis 3, Missouri, entered as second class matter January 23, 1917, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Additional entry authorized at Jefferson City, Missouri. Subscription Price: United States, its Possessions, Pan-American Countries, $10.00; In Canada and other Foreign countries, $11.50. Printed in the U. S. A.

American Heart Journal

VOL. 35 MARCH, 1948 NO. 3

Original Communications

THE EFFECT OF OCCLUSIVE ARTERIAL DISEASES OF THE EXTREMITIES ON THE BLOOD SUPPLY OF NERVES. EXPERIMENTAL AND CLINICAL STUDIES ON THE ROLE OF THE VASA NERVORUM

JOSEPH THOMAS ROBERTS, M.D., PH.D.
LITTLE ROCK, ARK.

WITH THE TECHNICAL ASSISTANCE OF W. H. JARVIS, R. S. BROWNE, F. D. SPENCER, JR., JULIAN KEY, J. A. RIVAS, AND D. BRANDT

ISCHEMIA of peripheral nerves has received little attention from physicians. Except as a nerve may reflect changes in the skin, muscles, and nerve endings affected by ischemia, the blood supply of peripheral nerves has been thought to be of little importance by most physiologists. The anatomy of the blood supply of nerves has been described by many authors, but even this knowledge is not generally recalled in connection with clinical problems. It is common belief that the metabolism of a peripheral nerve depends upon the cell bodies of its neurones rather than upon the nourishment of its axones.

For about twelve years, [1-4] have been studying the problem of the role of the vasa nervorum under both clinical and experimental conditions. The find-

The work described in this paper was done in part under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Texas. The illustrations and sections were made at the Army Institute of Pathology.

Presented at the Twentieth Scientific Meeting of the American Heart Association, Atlantic City, N. J., June 6 and 7, 1947. (Also, in part, before the Galveston County, Texas, Medical Society on Oct. 31, 1941, and Feb. 8, 1943; the Medical Society of the District of Columbia as the Davidson Lecture, Oct. 17, 1945; the Society for Experimental Biology and Medicine, Washington, D. C., Dec. 6, 1945; the American Association of Anatomists, Cleveland, Ohio, April 6, 1946; and the American Medical Association, Section on Nervous and Mental Diseases, Atlantic City, N. J., July 11, 1947.)

From the University of Arkansas School of Medicine, Department of Medicine, Little Rock, Ark. The earlier work was conducted at Gallinger Municipal Hospital, Georgetown University, George Washington University, Washington, D. C., and the University of Texas Schools of Medicine, Galveston, Texas.

ings indicated that ischemic nerves suffered changes in function and structure. After our work was well under way, several publications of importance in this field appeared in this country and abroad, stimulated possibly by the interest in injuries of peripheral nerves in war casualties.

Aviation and submarine aeroembolism suggested certain techniques to me. My experiments have consisted of interference with the blood supply of peripheral nerves in various ways under both acute and survival conditions. Clinical cases have been collected where the influence of ischemia on a peripheral nerve could be demonstrated by dissection and injection.

EXPERIMENTAL STUDIES

Acute Experiments.—Confirmation of previous reports concerning the anatomy of the blood supply of normal peripheral nerves was obtained by injecting dye (either Chicago blue, 2 per cent, or India ink diluted with equal parts of saline) into the aorta of normal dogs at pressures of 100 to 120 mm. Hg before sacrificing the animal. The nerves were then carefully removed and fixed in 10 per cent formalin. Also, nerves from the normal limbs of the dogs with experimental lesions were studied in the same way. It was found by clearing and dissection that there is a rich blood supply to each nerve (Figs. 1 and 3,*A*). This blood supply consists of a finely meshed plexus of capillaries, precapillaries, arterioles, and venules distributed longitudinally in the perineurium within the central part of a nerve and between the axones. This intrinsic plexus arises from another coarser plexus in the epineurium or fibrous sheath that surrounds the nerve. This coarser plexus corresponds to the plexus in the pia mater of the spinal cord and brain. It consists of one or sometimes more coarse longitudinal vessels anastomosing with segmental nutrient arteries which come from blood vessels in the neighborhood. Thus, there is both a longitudinal and segmental arrangement of the blood vessels in the epineurium. The origin of the nutrient arteries from neighboring vessels is subject to variation in different cases. Veins accompany the arteries. The nutrient arteries and some of those within the nerve have a well-defined muscular media, suggesting that the flow of blood through the vasa nervorum is subject to vasomotor autonomic control. The distance between the nutrient arteries also varies, but is usually between one and three inches for the larger named nerves. With smaller nerves, the segmental vessels enter at shorter intervals. Every nerve is nourished by small vessels. Even a single strand nerve in the skin is accompanied by a capillary network; this was seen in a transparent chamber grafted (for "visualization" of vessels and nerves) into a rat's back by Dr. G. H. Algire, of the National Cancer Institute.

To occlude the blood supply of a peripheral nerve, several procedures which would impair the blood supply in ways simulating clinical conditions were applied to the sciatic nerve of normal adult dogs (Fig. 2). Control experiments consisted of exposing a sciatic nerve in exactly the same way as in these procedures but with omission of the devascularizing procedure. In five such control experiments no changes from normal were found on testing the function of

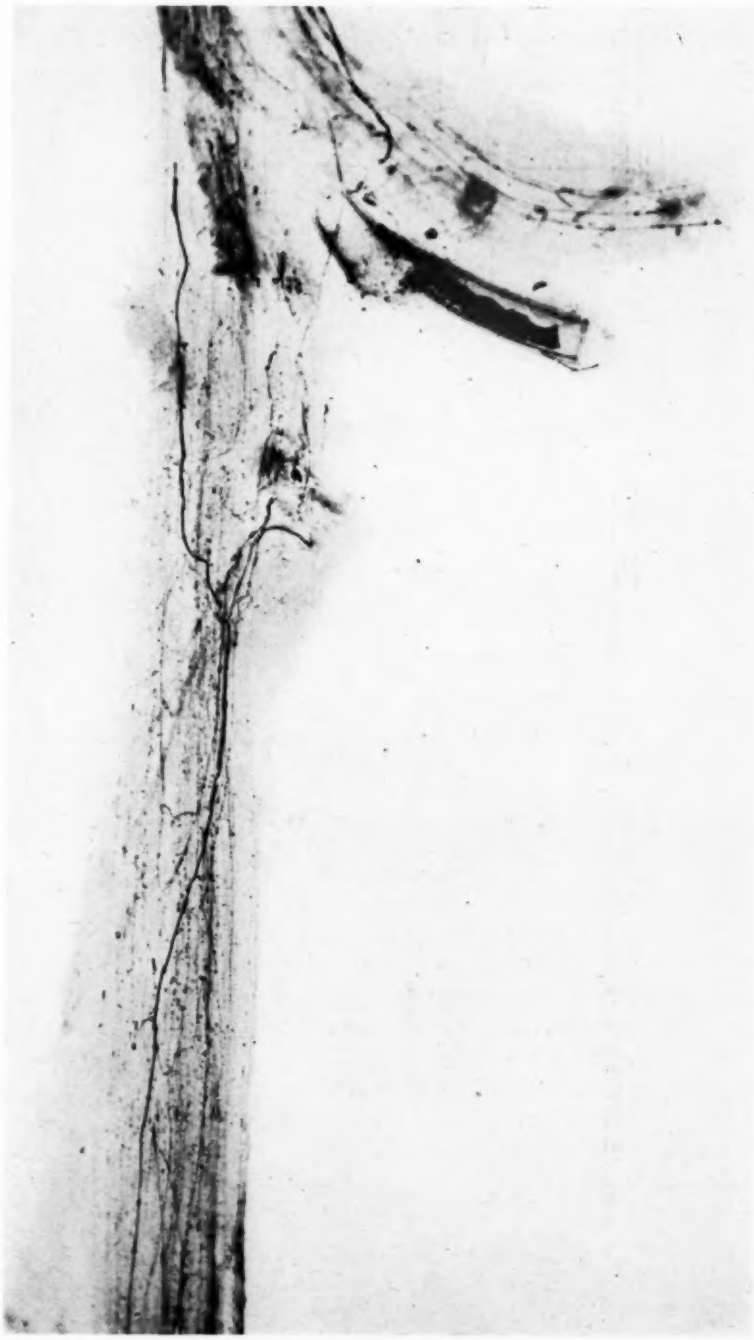


Fig. 1.—The larger vasa nervorum filled with graphite suspension which was injected into a segmental nutrient artery. Note the epineural plexus, longitudinal channels, and deeper, smaller anastomosing vessels. (Dog's sciatic nerve, cleared.)

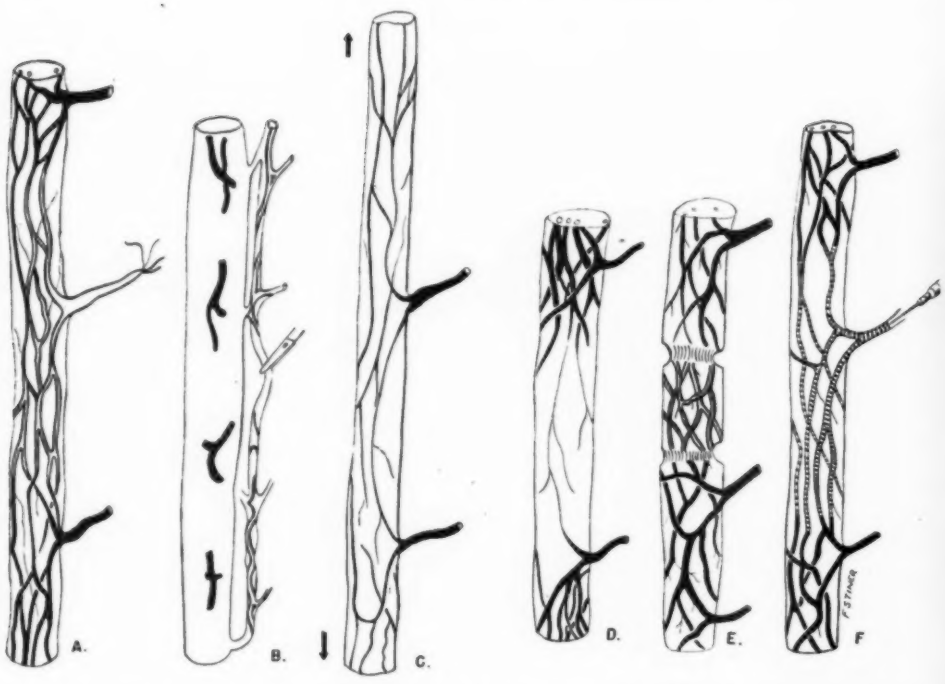


Fig. 2.—Diagrams of procedures for producing ischemia of nerves by obliterating the vasa nervorum. *A*, Ligation of a nutrient artery. *B*, Stripping the epineural plexus. *C*, Stretching a nerve. *D*, Tourniquet. *E*, Compression by two ligatures or pinching with hemostats. *F*, Embolism by injecting Lycopodium spores, graphite, or air.

the nerve, in the sections, or in the degree of injection by dye. The devascularizing experiments were as follows:

(*1*) *Ligation of a Segmental Nutrient Artery* (Figs. 2,*A* and 3,*B* and *C*): As in all of the following experiments, the sciatic nerve was exposed by careful dissection during anesthesia with nembutal given intravenously. The field was kept moist with normal saline at 37° centigrade. A segmental nutrient artery was divided between ligatures without any trauma or handling of the nerve. Chicago blue dye was then injected into the aorta and the animal was sacrificed. Before injection of the dye, no change in the function of the nerve was demonstrated when the tendon reflexes and response to heat, pinching, or electrical stimulation of the nerve were tested.

As shown diagramatically in Fig. 2,*A* and in the photographs in Fig. 3,*B* and *C*, the blue dye filled the vasa nervorum in this region with a patchy irregular distribution. In the region of the nerve supplied by the ligated segmental nutrient artery, blood remained in a number of the vasa nervorum, giving an intermingled red and blue coloration of the nerve.

Histologic sections showed no constant abnormalities.

(*2*) *Stripping the Perineurium* (Figs. 2,*B* and 3,*D* and *E*): In other animals, the left sciatic nerve was carefully exposed by the method previously de-

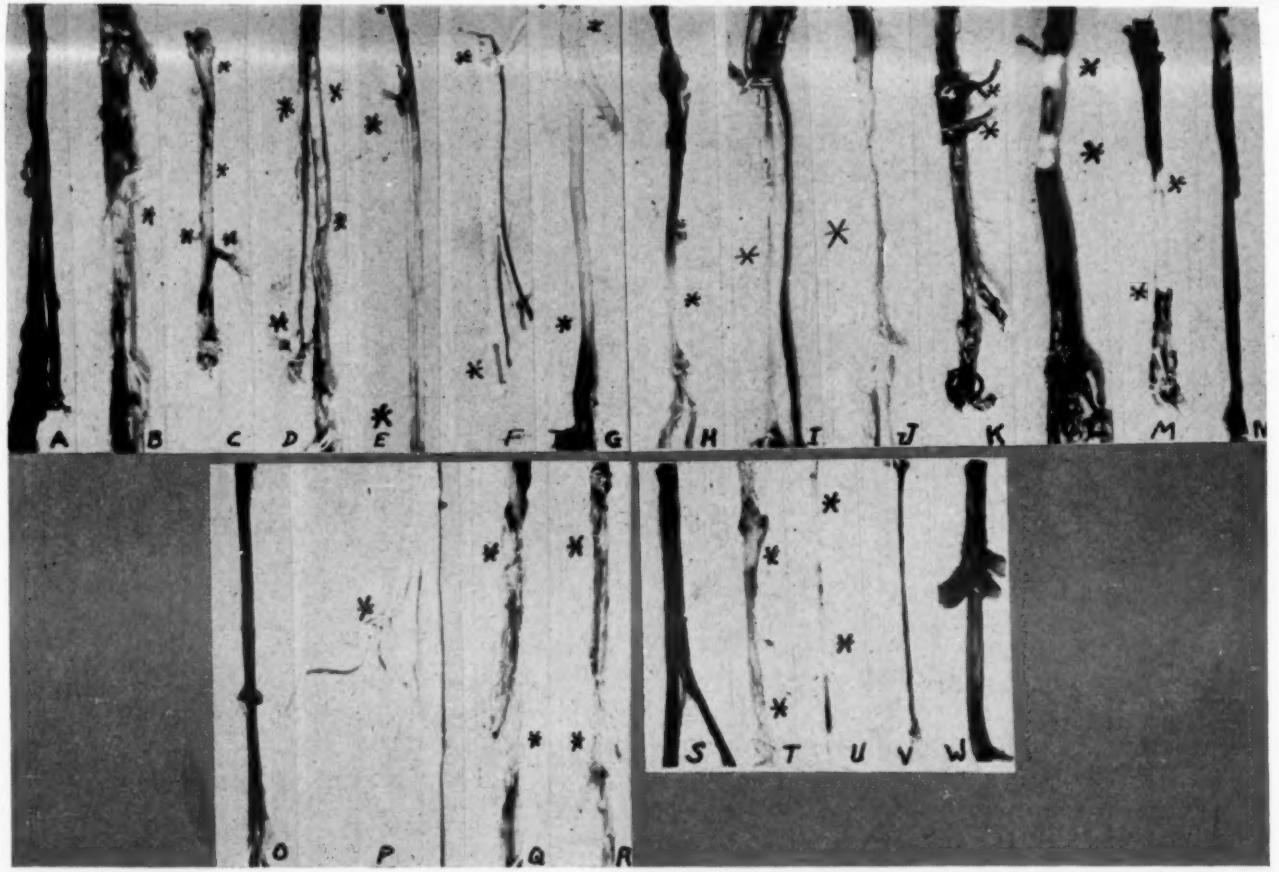


Fig. 3.—Vasa nervorum in normal and ischemic sciatic nerves (dogs), injected through the aorta with dye. *A*, Normal. *B*, Nutrient artery tied. *C*, Four nutrient arteries tied. *D*, *E*, Epineurium stripped off. *F*, *G*, Nerve stretched. *H*, *I*, *J*, Constricted by tourniquet around thigh. *K*, *L*, Ischemia between ligatures 10 and 20 mm. apart. *M*, Ischemia between levels pinched by hemostats. *N*, *O*, Normal. *P*, Embolism by Lycopodium spores in sciatic branch of inferior gluteal artery. *Q*, *R*, Aeroembolism of vasa nervorum. *S* to *W*, Segmental ischemia from embolism of left femoral artery by spores. *S*, Normal left sciatic nerve. *T*, Ischemic left common peroneal nerve. *U*, Ischemic left femoral nerve; *V*, normal right femoral nerve; *W*, normal right sciatic nerve. (Lesions marked by *.)

scribed and its perineurium stripped away very carefully with finely pointed forceps. Pinching or stretching the nerve fibers inside the epineurium was avoided. The blood vessels in the epineurium were pinched away in such a way as to cause no visible hemorrhage in the nerve. In these twelve animals where the epineurium was stripped away over a distance varying from 1.0 to 3.0 cm., no change was noted on testing tendon reflexes, sensibility to heat, pinching, or electrical stimulation.

When dye was injected into the aorta, the nerve was quite ischemic on its surface in the region from which the epineurium had been removed. Because of the presence of blood supply in the central part of the nerve, as a result of the longitudinal anastomoses above and below, there was a patchy and variable amount of dye in the stripped segment.

This experiment indicated that the plexus of vessels in the epineurium is important for maintaining an intact blood supply in a nerve, but that partial vascularity may be retained despite its absence over a short segment.

(*3*) *Stretching the Nerve:* In six dogs the left sciatic nerve was stretched in its longitudinal axis by traction upon the lower limb after all structures at the knee joint had been severed with the exception of the nerve, the popliteal artery, and its accompanying vein. Spreaders were placed between the femoral condyles and the tibial head so that these two structures were separated by a distance of one to two centimeters. Dye was then injected into the aorta and the animal sacrificed.

The vasa nervorum of the left sciatic nerve were obliterated by the stretching so that no dye entered the stretched segment (Figs. 2,*C* and 3,*F* and *G*). This ischemic or uninjected stretched nerve, when compared with the normally injected nerve of the opposite limb, as was done in the other experiments, showed a very striking difference in color. The stretched nerve was white, the normal one blue. Some of the small side branches of the sciatic nerve were not stretched by the procedure, because of the angle of their branching, and they were well injected. After the stretching was released during removal of the nerve for clearing, some dye flowed into the previously stretched vasa nervorum, apparently due to the effects of capillary pressure in these small vessels.

This experiment showed that the vasa nervorum may be obliterated by stretching, just as the lumen of a rubber tube may be occluded by stretching the tube.

(*4*) *Constriction by a Tourniquet:* In six animals a tourniquet of rope one-fourth inch in diameter was placed around the middle of the right thigh in such a way as to compress all structures at that level except the femoral artery and vein, which were outside of the tourniquet. The tourniquet was then tightened and dye was injected into the aorta before the animal was sacrificed.

The cleared nerve from this extremity was uninjected or ischemic at the level inside the tourniquet and poorly injected or partly ischemic for several centimeters above and below the constriction (Figs. 2,*D* and 3,*H* and *J*).

These experiments showed plainly that the blood supply of the nerve can be obliterated effectively by compression of the limb with indirect pressure upon the nerve itself. Such pressure resembles that on a nerve in a patient who ha a tumor, adhesion, dislocation, arthritic spine, faulty posture, or other condition where pressure on a nerve obliterates its blood supply.

(*5*) *Constriction of the Nerve:* Two ligatures were tied around the left sciatic nerve at intervals varying from 10 to 30 mm. in seven dogs. In some cases, a split rubber tube was placed around the nerve under the ligatures to prevent cutting of the nerve. Various degrees of constriction of the nerve were used.

Dye injected into the aorta filled the vasa nervorum of the nerve above and below the segment between the ligatures (Figs. 2,*E* and 3,*K* and *L*) as well as in the normal nerve of the opposite limb. No dye entered the vasa nervorum between the ligatures even in the specimens where the constriction with the ligature was slight. Between the ligatures, red blood was trapped, causing the opacity between the two ligatures seen in the photographs.

In three other animals the left sciatic nerve was clutched between the jaws of a hemostat at two points preceding the injection of dye into the aorta. Although the hemostats had been removed before the injection, no dye entered the vessels of the nerve between the two points clutched with the hemostat (Figs. 2,*E* and 3,*M*).

These two types of experiments indicated that the blood supply of a nerve can be destroyed by interference with the longitudinal anastomoses in the nerve, and that constriction of a nerve can obliterate its blood supply.

(*6*) *Embolism of the Vasa Nervorum:* The vasa nervorum were occluded by injecting a nutrient artery of the left sciatic nerve with emboli of particulate material. This consisted of Lycopodium spores,* powdered graphite, or air. In each case the emboli filled the small blood vessels within the central part of the nerve as well as in the epineural vessels and the nutrient arteries. When dye was injected into the aorta, none of it reached the portion of the nerve supplied by the obliterated vasa nervorum.

In seven dogs, when the suspension of Lycopodium spores was injected into the left inferior gluteal artery (ligated above and below the origin of its nutrient artery to the nerve to prevent embolization of collateral vessels), the nearby portion of the left sciatic nerve became devoid of blood, became white, and remained so even after injection of the blue dye into the aorta (Figs. 2,*F* and 3,*P*).

When air was injected into the nutrient blood vessels of a sciatic nerve in five dogs, the discoloration after the aortic injection of dye was very patchy and irregular (Figs. 2,*F* and 3,*Q* and *R*), as contrasted with a homogeneous discoloration of a normal nerve and the complete absence of dye in the nerve after devascularization by Lycopodium spores or other emboli. Five large white rats were placed in a chamber with pressure simulating an altitude of 12,000 feet.

*A freely flowing suspension of Lycopodium spores was prepared by shaking the spores in ether for a few minutes, filtering, and then suspending the spores in five to ten parts of normal saline. This prevented the adherance of the spores and blocking of the syringe as encountered otherwise.

When they were removed and the sciatic nerves rapidly exposed, the vasa nervorum were filled with small bubbles of gas.

These two experiments showed that aeroembolism can obstruct the vasa nervorum.

In another dog (Fig. 3,*S, T, U, V,* and *W*), Lycopodium spores were injected into the left external iliac artery. As a result, there was obliteration of the vasa nervorum of the left femoral nerve and of the left peroneal and other nerves below the knee which derived their blood supply from the popliteal and other branches of the femoral artery. However, the left sciatic nerve was as well injected with dye as were the right sciatic, the right femoral, and other nerves of the normal opposite limb.

This result was of value in showing that the longitudinal anastomosis within the sciatic nerve was inadequate for maintaining nourishment to the nerves below the knee, although apparently adequate for nourishing the nerve between the knee and hip joint under these circumstances.

Survival Experiments.—In twenty-three dogs the left sciatic nerve was exposed during anesthesia with nembutal, and procedures of the types which have been described were carried out aseptically; every effort was made to avoid injury to the nerves or surrounding structures. After replacing the muscle and closing the skin, the animal was allowed to recover consciousness and survive for one to seven weeks before dye was injected into the aorta and the animal sacrificed. During the survival period the functions of the nerve were frequently tested.

Results with several methods of attempting chronic devascularization of nerves were as follows:

(*1*) *Ligation of Nutrient Arteries:* In five dogs, when only a single nutrient artery or part of the nutrient arteries between the hip and knee joints had been ligated, no clinically discernable evidence of dysfunction of the sciatic nerve was found. In three dogs, when all nutrient arteries coming to the sciatic nerve between the hip and knee joints were destroyed, weakness of the extensor muscles of the foot and hamstring muscles was noted. Changes were not as marked, however, as in the studies which will be described. Histologic study revealed only occasional degenerated axones, especially near the periphery of the nerves.

(*2*) *Stripping of the Perineurium:* When the epineurium had been carefully stripped away for only 1.0 to 3.0 cm. in five dogs, no changes in function of the nerve were noted. When the epineurium was stripped away from all or most of the segment of nerve between the hip and knee joints in four dogs, impaired function of the nerve was shown by weakness of the extensor muscles of the foot and in the hamstring group of muscles, by footdrop with trophic ulcers on the dorsal surface of the foot, and by partial or complete loss of sensibility to pinpricks, pinching, or heat. Histologic study revealed degeneration of many axones, especially those with large myelinated sheaths; axones near the periphery of nerve bundles were affected more than those in the central part of the nerve.

Fig. 4.—Hind limbs one week after embolism (spores) of left sciatic vasa nervorum. *A*, Toedrop, inverted foot, atrophied calf and hamstring muscles, necrotic spots on skin. *B*, Trophic ulcers on dorsum of toes. *C*, Hyperflexed ankle.

(*3*) *Stretching of the Nerve:* No survival experiments of this type were completed. Because it was not possible to obtain longitudinal stretching of the nerve without severing the knee joint, studies during survival would have been difficult to evaluate. Stretching of the nerve by lateral displacement was performed but the results were equivocable because injury might have been done to the axones of the nerve and also because the blood supply returned to the nerve after stretching was released and the nerve allowed to shorten to its original length.

(*4*) *Compression of the Nerve:* For the reasons just stated, studies were not made during survival after clamping the nerve with hemostats or compressing it by ligature or tourniquet. In such experiments, we could not distinguish between the effects of injury to the axones and injury from anoxemia of ischemia.

(*5*) *Embolism of the Vasa Nervorum:* In seven dogs in which obliteration of the vasa nervorum was obtained by injection of sterile graphite or Lycopodium spores into the nutrient artery of the left sciatic nerve, evidence of impaired function of the nerve was found as soon as the animal recovered from the anesthesia. In these animals, loss of strength of the hamstring muscles of the thigh, the leg muscles, and those of the foot was so great that the animal (Fig. 4) seldom tried to use the affected limb for running except when fatigue made it necessary. Likewise, sensibility to painful pricking, pinching, or heat was lost over the area supplied by the branches of the devascularized sciatic nerve. Patellar reflexes were hyperactive and ankle jerk reflexes were absent. After intervals of a few days to two weeks, loss of tone and severe wasting of the muscles supplied by the devascularized sciatic nerve became evident, as did the appearance of trophic ulcers on the dorsum of the left hind foot due to pressure from running or standing on the left extremity after the development of the toe drop (Fig. 4,*B*). Vesicles and spots of dry gangrene developed in the skin of the dorsolateral aspect of the thigh adjacent to and below the incision and also of the leg. These changes were thought to be due to loss of innervation of the skin from branches of the sciatic nerve. Another less likely possibility is that the emboli passed into the small blood vessels of the skin through anastomoses with the other nutrient arteries.

When these animals were sacrificed during injection of blue dye into the aorta, nerves were uninjected in the region below the earlier devascularization by embolic material. Histologic examination revealed degeneration of the nerve below this site just as though the nerve had been cut.

CLINICAL OBSERVATIONS

Evidence of obstruction of the vasa nervorum was found in patients suffering from a wide variety of conditions, either by inspection of the dissected nerves or after injection of dye into the popliteal artery of limbs amputated from necessity. Examples of such cases follow:

(1) A patient with subacute bacterial endocarditis showed numerous embolic phenomena affecting the brain, lungs, kidney, spleen, eye, and skin, and developed foot drop with evidence

of paralysis of the left peroneal nerve. There was also impaired sensation to touch, pain, temperature, and vibration on the lateral aspect of the left foot and toes. Autopsy revealed large friable vegetations on the mitral valve with infarctions in the organs named. Careful inspection of the left peroneal nerve revealed petechiae and thrombosis of the vasa nervorum in the middle of the nerve, due to obstruction of the nutrient arteries of the nerve by a small embolus.

(2) A woman with a one-year illness of unknown cause had had septic fever, severe anemia, weakness, and cachexia for several months. Several days before death, she suddenly developed an inability to flex the left hip joint and extend the left knee. At autopsy the only abnormalities found were a small denuded roughened area of the mitral valve which resembled the base from which a vegetation had been separated recently and a hemorrhagic area 2.0 cm. long in the left femoral nerve. The nutrient artery supplying this section of the nerve was occluded by a small embolus. This embolus was part of the vegetation which had broken away from the mitral cusp.

(3) During repair of a man's right femoral hernia, injury to a nearby nutrient artery of the femoral nerve occurred. This nutrient artery was divided between ligatures. After recovery from anesthesia, the man was unable to extend his right knee and had no sensation for touch on the anterior right thigh for five weeks, after which time these functions gradually returned. The injury to the blood supply of the right femoral nerve accounted for these defects.

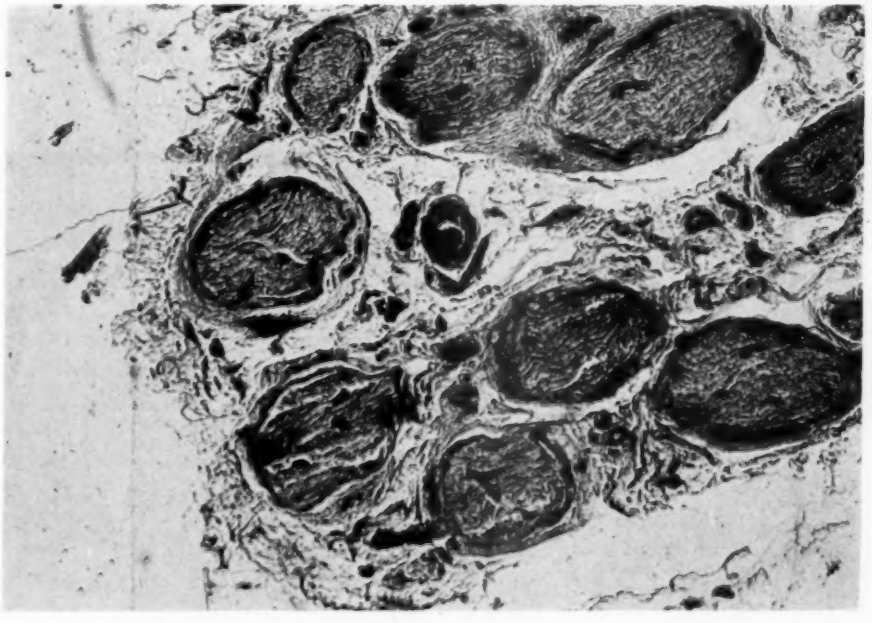
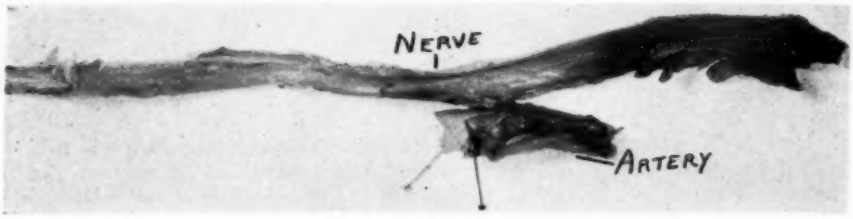


Fig. 5.—Thrombosed vasa nervorum of left plantar nerve, with degeneration of nerve fibers. Case 4.

(4) A man with myocardial infarction suddenly developed pain in the large toe and medial portion of the foot. These parts became pale followed by reddish purple discoloration. Pain as well as the power of sensation disappeared two days later. Despite paravertebral lumbar sympathetic block with novocaine and refrigeration therapy, gangrene of the toe and foot developed which required mid-thigh amputation. Careful dissection of the vessels and nerves revealed embolism and thrombosis of the dorsalis pedis and medial plantar arteries, with thrombosis of the anterior tibial artery and the accompanying veins. Thrombosis of the vasa nervorum of the medial plantar nerve was also found (Fig. 5). These findings indicated that the initial pain was due to partial or early ischemia of the involved nerves, with disappearance of pain and sensation after the thrombosis of the vasa nervorum had become complete or had endured long enough for degeneration of the axones to occur.



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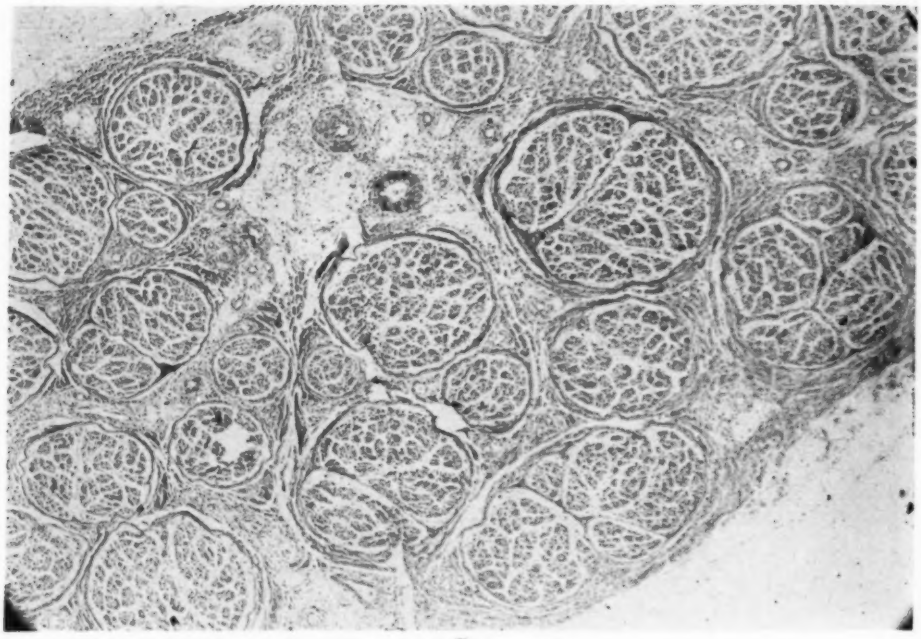

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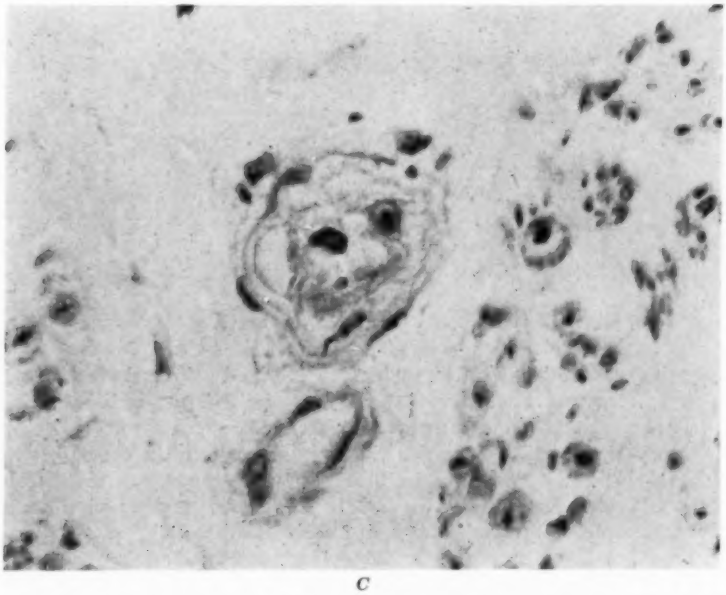

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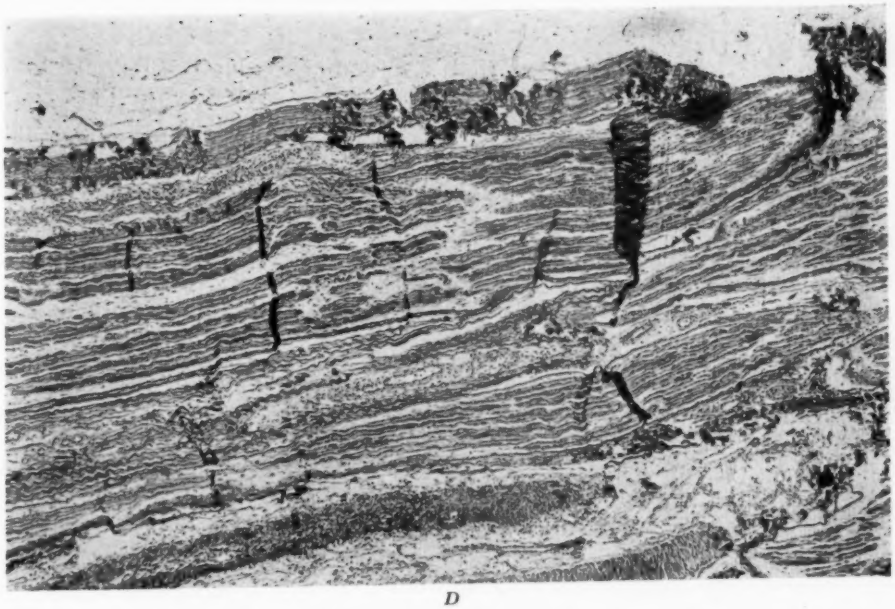
Fig. 6.—Case 5. (*A*) Ischemia of left tibial nerve (pale lower part) with good injection with dye (dark upper part) in vasa nervorum above level of thrombosis in posterior tibial artery and its neural branches.

(*B* through *F*) Sections of ischemic portions of this nerve. Note: absence of dye, thickened walls of arterioles and capillaries, fibrosis, and patchy degeneration of nerve fibers. Hematoxylin—eosin.



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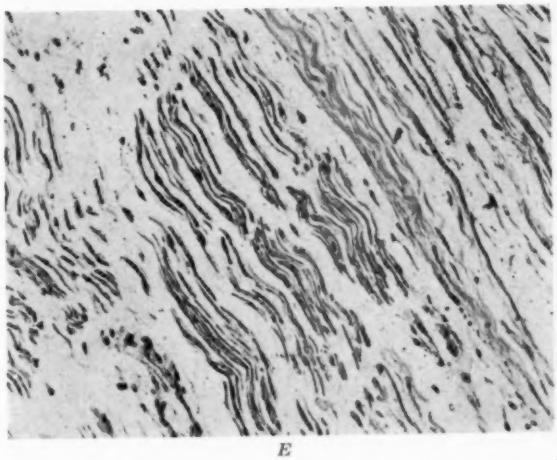

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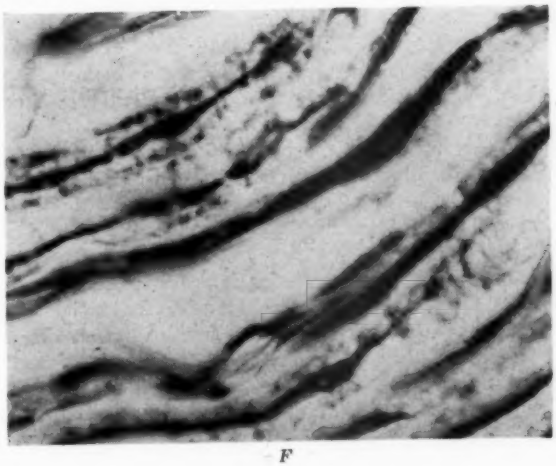


F

Fig. 6—Cont'd.

(5) A middle-aged man with diabetes developed gangrene of the left first and second toes. He had anesthesia of the plantar surface of the foot and could not flex the toes. Mid-thigh amputation was required. The popliteal artery was injected with Chicago blue dye; dissection of the vessels and nerves was then carried out. A thrombus occluded the mid-portion of the sclerotic posterior tibial artery. The accompanying tibial nerve was well injected with dye above the level where the artery was occluded by the thrombus. Below this level the nerve (Fig. 6) was white and free of dye except for a small portion about 1.0 cm. in length supplied by a patent nutrient artery that apparently received its blood through collateral anastomoses from the lower middle part of the less severely sclerotic peroneal artery. The lower part of the anterior tibial artery was sclerotic but not occluded, and the peroneal nerves were quite well injected. The changes in function were due to ischemia of the lower tibial nerve. The small vessels were nearly or entirely occluded by proliferation or thrombosis, with loss of many axones and myelin sheaths (Fig. 6, *B* through *F*).

(6) An elderly woman with chronic rheumatic heart disease, atrial fibrillation, myocardial infarction, and thrombi in the left atrium and ventricle suddenly developed severe pain and pallor in the right foot and toes, followed by loss of pain and sensation over these areas. Gangrene of the dry type required supracondylar amputation. Several weeks later similar events affected the left foot, toes, and lower leg, with, in addition, loss of sensation of the lower leg and inability to flex or extend the left toes and ankle. When these two limbs were dissected after injection of the popliteal arteries, embolic and thrombotic occlusions of the sclerotic arteries were found at the level of the ankle in the right limb and about two inches below the knee in the left extremity. On the right side, the blood vessels of the nerves were well injected above the ankle but uninjected below that. On the left, the nerves were ischemic, as shown by injection, below the point of arterial occlusion in the upper third of the leg. The branches of the nerves going to the skin and muscles in the right leg arose above the thrombosis, while in the left leg the nerves to these structures came from below the level where the two branches of the sciatic nerve were devascularized by the thrombi. These findings explain the difference in neurological abnormalities of the two limbs; the ischemia of the nerves developed at different levels. Since the innervation of the flexors and extensors of the left toes and ankle was from devascularized nerves, power of movement of these parts was lost on the left but retained on the right side where the nerves were ischemic only below the origin of branches to the muscles moving the toes and foot.

(7) In other similar cases, injection of dye into the popliteal artery of amputated legs revealed poor injection of the blood supply of the nerves in portions supplied by thrombosed arteries or vessels obliterated by proliferative lesions. In two patients with extensive phlebothrombosis of the foot and leg, retrograde propagation of the thrombus had obliterated the blood supply of the peroneal and tibial nerves. These patients had shown loss of sensation over the foot and toes, with loss of ability to move the toes after an initial period of severe pain of the foot and calf.

(8) A young man with chronic thrombosis of the inferior vena cava developed extensive dilatation of collateral anastomoses for the return of blood to the heart. On post-mortem examination, the venous vasa nervorum of both sciatic arteries were found to be enormously dilated. Some of these vessels in the sciatic nerves had lumina 2.0 mm. in diameter. This finding shows that another role of the vasa nervorum can be to serve as potential collateral circulation for the relief of obstruction in other vessels. I have not yet found any cases where the arterial vasa nervorum adequately served this function as the venous blood vessels of the nerves did in this case. However, such an occurrence might be expected to happen occasionally, especially during embryonic or even early postnatal life. At these stages the arteria comitans nervi ischiadici approaches the obturator and femoral arteries in size, only to become insignificant in size with later growth.

(9) During a recent supracondylar amputation, it was noted that the femoropopliteal artery was closed by sclerosis and thrombosis so that it did not bleed when cut and that rather troublesome bleeding from the cut sciatic nerve occurred. In this instance the sciatic vasa nervorum were serving as partial, though insufficient, collaterals for the obstructed major artery. This 48-year-old woman, without diabetes, suddenly developed pain in the foot, but after two days had no pain, sensation, or power of motion in the foot, toes, and lower leg. The foot and toes became cold, black, and shrivelled, and the skin of the front and back of the leg developed large

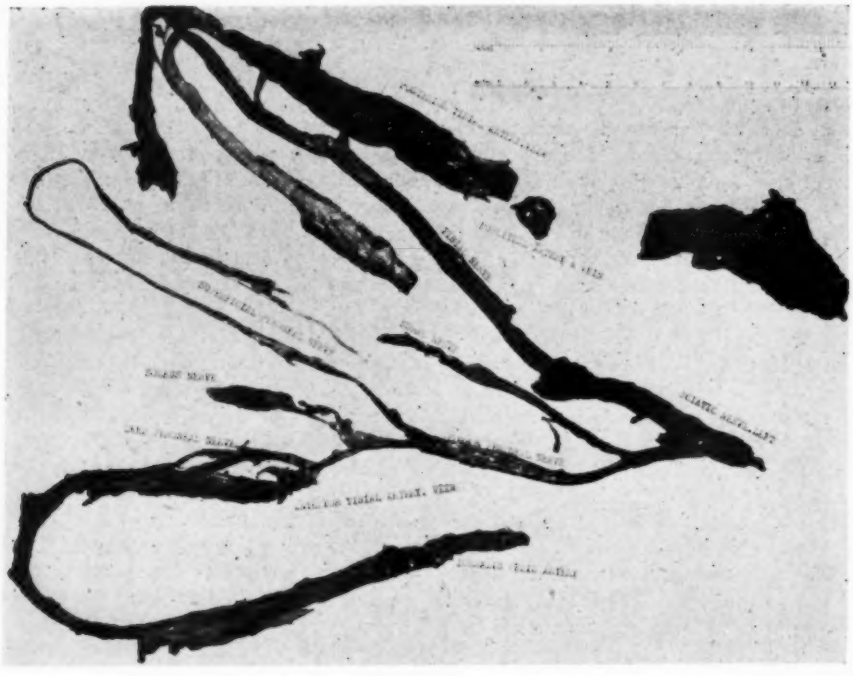
vesicles. Dye injected into the amputated popliteal artery below its occlusion filled the vasa nervorum of the sciatic nerve and upper parts of its branches very well. At about the middle of the posterior tibial artery there was a firm, attached thrombus. The tibial nerve at this level appeared hemorrhagic, but below this level, was white and free of any dye. Other arteries and veins had partially occluding thrombi, and the other nerves were injected with dye only in irregular patchy areas. In some places, the thrombi in the vasa nervorum were plainly visible (Fig. 7). Many sections from this limb, as in the others already described, were stained with several methods (for example, Masson, Weil myelin, Bodian-silver impregnation, hematoxylin-eosin, Mahon myelin). Severe intimal proliferation, elastic fragmentation, eccentric atheromata, luminal reduction, thrombosis, extravasation of blood, moderate to marked demyelinization, and necrosis of nerve fibers were seen in many sections at levels where dye was absent. In levels where the dye was well injected, these changes were missing or strikingly less. The arteriolar and capillary changes were seen in epineural, perineural, intrafascicular, and interfibrillar vessels. Perifascicular or perineural tissue was excessive in the ischemic areas. Even the vasa nervorum of the nerves in the walls of the thrombosed posterior tibial artery were thrombosed.

(10) Segmental ischemia of a sciatic nerve was seen during an exploratory operation for relief of extreme pain with paralysis of several months' duration in a young man with syphilis. This began a few minutes after a bismuth preparation was injected into or near the sciatic nerve instead of intramuscularly. During operation, dense fibrous adhesions constricted the nerve and obliterated its vasa nervorum. These adhesions were removed as carefully as possible. Pain was relieved and in time the paralysis improved partially. Syphilis probably played no role in this vasoneuropathy. Distinction between effects of ischemia and constriction of axones by the adhesions is difficult.

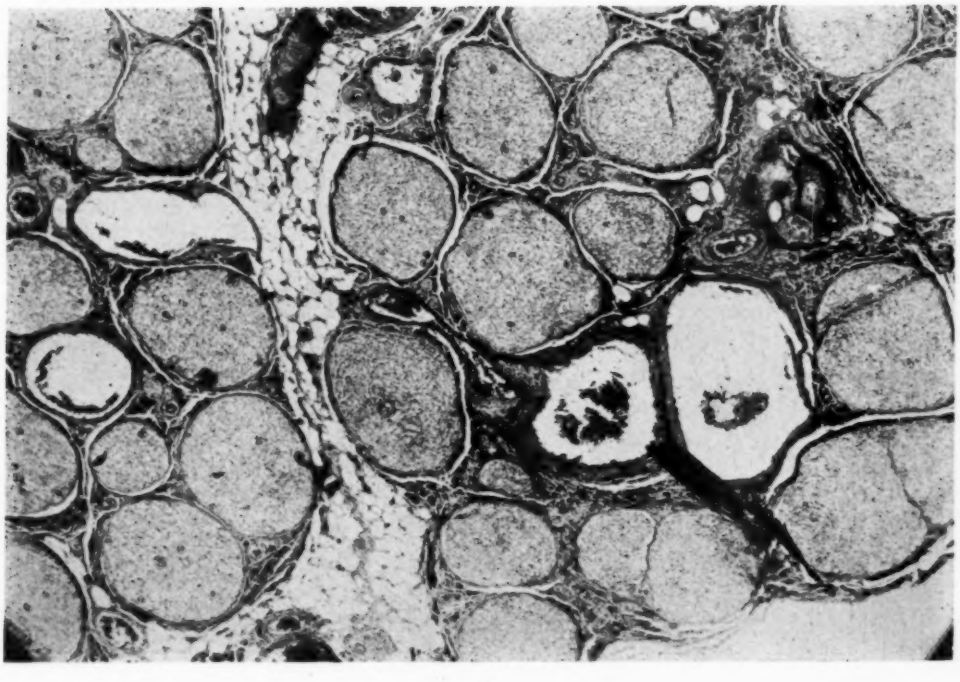
(11) Observations on myself consisted of noting the effects of compressing the radial, sciatic, sural, common peroneal, or plantar nerve against a firm surface, or by hyperabducting the arm, until the onset of tingling, numbness, pain, or weakness of muscles. When the compression was removed, normal sensation returned progressively over a period of one to three minutes in a steplike manner. With each pulse beat, the symptoms improved a little more until normal sensation and motion were possible. This suggests that the symptoms were due to ischemia from obliterating the vasa nervorum. If the axones had been injured, the restoration to normal would be expected to take a much longer time and not to have the phasic improvement related to each pulse.

LITERATURE

The literature on the blood supply of the nerves has been thoroughly reviewed in recent years by Adams,[5] Sunderland,[6-8] and Fetterman, Spitler, and Roberts[1]; therefore repetition of this is not necessary. Isenflamm and Doerffler[9] in 1768 seem to have been the first to ascribe importance to the vasa nervorum in the causation of various peripheral nervous disorders. Most of the reports have dealt with the anatomic distribution of blood vessels in various specific nerves or with hypothetical discussions of the possible role of the blood supply of the nerve in accounting for the symptoms in patients with vascular diseases. Relatively little actual experimental work on the subject has been found reported in the literature. In 1905 Okada[10] described degeneration of the sciatic nerve in rabbits after ligating the inferior gluteal artery. Koch,[11] also working with rabbits, observed that a blood supply is necessary for a normal current of injury in the nerve. Adams[5] in 1943 repeated the experiments of Okada but found that ligation of the inferior gluteal artery did not result constantly in degeneration of the sciatic nerve unless manipulation with possible injury of the nerve also occurred. Bentley and Schlapp[12] obliterated the blood supply of nerves by pressure with mercury-filled bags and found that the ability of the nerve to con-



A



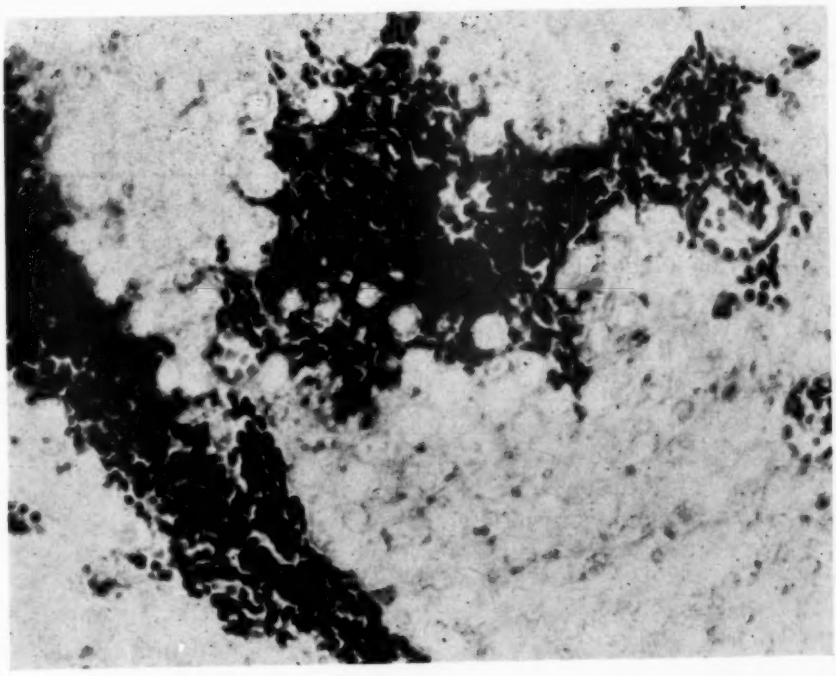
B

Fig. 7.—Case 9. (*A*) Dissection of nerves and vessels of left leg, after injection of dye in popliteal artery. Contrast well-injected sciatic and upper tibial nerve with ischemia of lower tibial nerve below thrombosis of posterior tibial arteries and its neural branches. Ischemia of superficial peroneal nerve also, below thrombosis of dorsalis pedis artery.

(*B*) Section of ischemic portions of tibial nerve. Myelin and Masson stain.

(*C*) Section of ischemic portion of tibial nerve, with extravasation of blood from occluded vasa nervorum, and surrounding this, areas of degenerating axone cylinder and myelin sheaths. Weil myelin stain.

(*D*) Dilated vasa nervorum in sciatic nerve at level of amputation, above injection.



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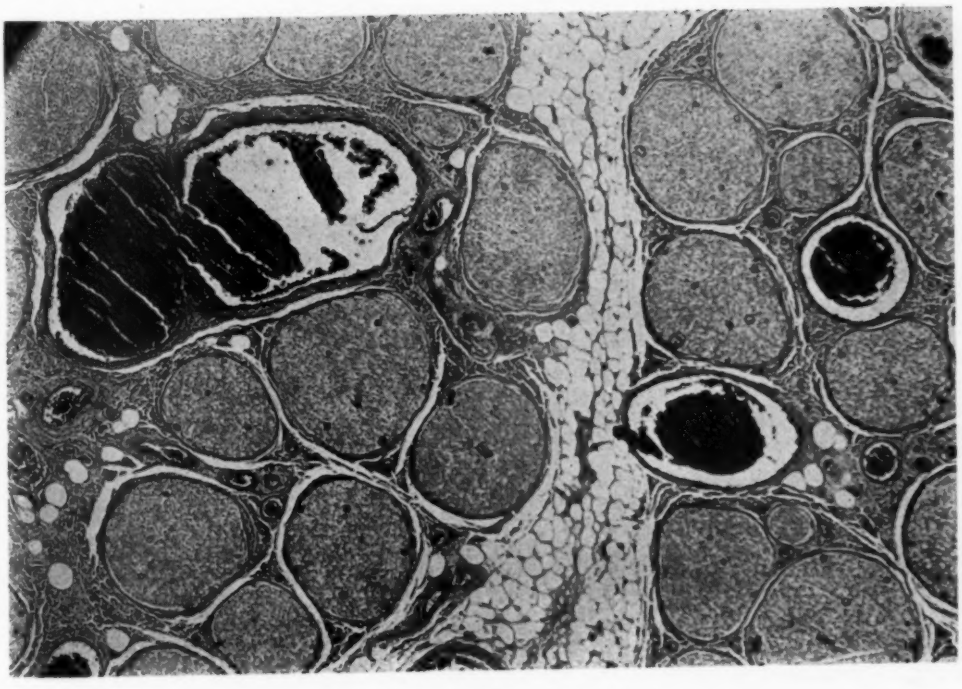

D

Fig. 7—Cont'd.

duct impulses was impaired by a pressure which was thought to be adequate for occluding the vasa nervorum without injury to the nerve itself. Denny-Brown and Brenner[13] believed that the lateral peroneal nerve was more susceptible to injury by being pressed against the fibula, because this nerve suffered more from ischemia produced by a tourniquet than did the medial peroneal nerve.

The effect of local ischemia upon human nerve fibers in vivo has been studied by Thompson and Kimball[14] and very recently (since my work was done) by Kugelberg.[15] In both studies ischemia was produced by a compressing sphygmomanometer arm band. Thompson and Kimball reported that the threshold for sensation to electrical stimulation fell rapidly and progressively for the first twelve minutes of ischemia and then sharply rose. This indicates that ischemia of a nerve first increases and later diminishes the irritability of the nerve. Kugelberg, with the aid of electromyography, found that a local area of ischemia produced two forms of spontaneous activity: (1) that occurring during ischemia and consisting of isolated action potentials of irregular frequency; and (2) that seen after ischemia and consisting of repetitive discharges which occurred in bursts. When the nerve fiber ceased discharging, though the excitability was still high, a passing action potential discharged a burst of spikes and acted as a "trigger" of a trigger zone. This mechanism was easily fatigued. Both studies seemed to confirm the opinion of Lewis and associates[16] that such ischemia affects the nerve endings. These papers review the difficulties in distinguishing between the effects of compression and anoxemia of nerve fibers and especially cite the work of Bishop and associates[17] and of Gasser.[18] Wright[19] and De Takats[20] have recently renewed the interest in ischemic peripheral neuropathy.

I have found no reports of experimental interference with the blood supply of nerves in which injury to the nerve itself or to other tissues was as carefully excluded as in the acute and chronic experiments which have been described. Likewise, in previous studies there has not been as careful integration of clinical observations and anatomic findings in human nerves as has been carried out in these studies.

Ischemic lesions of nerves, resembling those found in the cases of this study, have been described by Woltman and Wilder,[21] Barker,[22] and by Priestly[23] in studies on patients with diabetes mellitus, thromboangiitis obliterans, and arteriosclerosis. These authors noted proliferative lesions in the vasa nervorum, especially those in the thickened perifascicular fibrous tissue, patchy necrosis of nerve fiber bundles, and various combinations of wallerian degeneration, fibrosis, edema, atrophy, lymphocytic infiltration, inflammation, and thrombosis of the vasa nervorum. The use of injection methods in their studies would have been of great value. Karnosh[24] has attributed sciatic causalgia to ischemia of the sciatic nerve. Fetterman and Spitler[1] discussed cases of trauma, embolism, arteriosclerosis, diabetes mellitus, Buerger's disease, periarteritis nodosa, syphilis, and polycythemia vera as examples of peripheral neuropathy attributable to ischemic vascular disease of nerves. Many other writers have mentioned in varying detail the concept of neuropathy due to a defective blood supply in various regions of the body, including the ear, eye, trigeminal ganglion, and extremities.

Vasoneuropathy is caused by frostbite, immersion, and trench foot, and possibly by burns. Thrombosed vasa nervorum are present in such states and may contribute to the clinical findings. There is lack of agreement on whether neural ischemia is cause or effect of other pathologic changes in frostbite and immersion foot, according to Friedman,[25] Denny-Brown and associates,[26] and Ungley and Blackwood.[27]

These papers are of great value, when considered in the light of the work reported here, in clarifying the mechanism of the findings and complaints in cases of causalgia, phantom limb, and thermal changes on the basis of occlusive or vasospastic neuropathy.

DISCUSSION

In the acute experiments described in this paper, it was shown that the blood supply of a nerve is very abundant and that this blood supply may be obliterated in a variety of ways which are analogous to the effects produced clinically by injury or disease in human beings. When the blood supply of a nerve was obliterated by ligating a single nutrient artery or the nutrient arteries of a small segment, only a partial or patchy ischemia usually occurred because collateral anastomoses through the longitudinal vessels in the nerve could maintain adequate nutrition. This belief that the longitudinal vessels have considerable importance in maintaining the function and structure of the nerve was corroborated by the survival experiments where ligation of segmental nutrient arteries only was carried out. This was in keeping with the clinical observation that single or several nutrient arteries may be ligated or obliterated without constant permanent injury to the function of a nerve during surgical procedures where a nerve is exposed, repaired, or transplanted. If the epineurium was stripped, with removal of the important longitudinal epineural plexus, the nerve was more ischemic in the stripped segment than in the normal nerve. In both the acute experiments and in the survival experiments of this type, there was more commonly evidence of disturbed function than in the group with ligation of single nutrient arteries. In such cases, nourishment of the nerve could occur only through the small vessels within the central part of the nerve and this relatively poor blood supply could make the nerve more susceptible to ischemia or injury from any other cause.

That stretching of a nerve could produce obliteration of the blood vessels in the nerve was clearly shown in the acute experiments performed in this study. Moreover, these results are of value in explaining the frequency with which nerve function is lost when nerves are stretched excessively during surgical procedures, by dislocations and faulty position, or by expanding tumors. This study shows that obliteration of the vasa nervorum by stretching of a nerve frequently occurs in man and is responsible for such clinical symptoms and findings as pain, numbness, tingling, paresthesia, weakness, paralysis, atrophy, hyper-reflexia, and other disturbance in the extremities. Such stretching can occur during prolonged unusual positions such as sitting with the legs crossed, keeping the arms elevated above the head or sleeping in an unusual position.

Closely related to this mechanism is closure of the vasa nervorum by compression of the nerve which may result from similar instances of unusual posture, (for example, pressure on the sciatic nerve by sitting on the edge of a chair, pressure upon a nerve during examination, sleep, or operation, and pressure by bandages, tourniquets, casts, or constricting types of clothing). The neurovascular syndrome, recently reviewed by Wright,[19] is probably due to ischemia of nerves caused by pressure on or stretching of the vasa nervorum. We have seen recently three patients with chronic tingling or pain in the hands and arms, especially along the ulnar side, after first awakening. In each case the radial pulse became obliterated at some point of extending, rotating, and abducting the shoulder. The symptoms were relieved by changing the customary habits of sleeping on the arm. As in Wright's cases, this favors the neurovascular explanation of the complaints.

The acute and survival experiments with injection of embolic material into the nutrient arteries establish the fact that removal of blood supply to a segment of a nerve without injury to the nerve itself may result in impaired function and structure of the nerve. In these experiments the small blood vessels throughout the nerve were occluded without compressing or stretching the axones and without allowing the opportunity for nourishment to occur by way of collateral anastomoses with longitudinal vessels or other segmental arteries. Such experiments have their homologue in human cases where embolism, thrombosis, or proliferative lesions in the vasa nervorum or in their source of blood supply result in ischemia of a peripheral nerve. On the basis of the acute experiments showing that air injected into nutrient arteries caused a patchy type of injection with dye, it is believed that aeroembolism can cause dysfunction of the peripheral nerves by partial obliteration of their vasa nervorum. In patients suffering from high altitude or decompression sickness, symptoms and signs indicate early involvement of peripheral nerves in many parts of the body (for example, nerves of the ears, eyes, muscles, and about the joints) which may be explained best as being due to partial ischemia of these nerves by aeroembolism.

Although the experiments and clinical investigations described in this presentation involved only the larger nerves of the extremities, I believe that the role of the blood vessels in every nerve of the body may be equally as important. On the basis of this reasoning, it is possible to explain many common or bizarre symptoms affecting localized areas, such as the ear or eye, or widely scattered areas throughout the body, as in a condition where ischemia of many widely scattered nerves could exist. Embolism from vegetations, mural thrombi or plaques in the aorta, gas bubbles, bacterial clumps, tumor cells, or fat particles may be distributed by the blood stream to the vasa nervorum in any organ or part of the body and so affect the nerve supply in that organ. Increased viscosity of the blood, resulting from dehydration, polycythemia, hyperglycemia, or other causes, and slowing of blood flow predisposes to thrombosis, and this can occur in the small blood vessels of nerves as well as in large vessels. Small nerves have their individual blood supply as well as large nerves, as can be seen in sections of injected material or by using a transparent chamber grafted into the skin of the rat's back.

There is little available knowledge regarding the role of the blood vessels in nerves of the sympathetic system. An analogy with the experiments (described here) on the somatic peripheral nerves suggests the belief that some dysfunctions of the viscera may be due, at least in part, to similar lesions affecting the vasa nervorum of the sympathetic nerves. Recently De Takats[20] has discussed this problem briefly in a report on proliferative arteriolar changes in the dorsal root ganglions of diabetic patients. The lymphatic vessels of nerves may also have an important role, but no studies of this are known.

On the basis of these experiments and observations on patients, it seems likely that acute occlusion of vasa nervorum may be accompanied at first by severe pain, paresthesia, or hypersensitivity, and may be followed later by disappearance of these abnormalities with possible anesthesia or paralysis. This may be due to hyperconductility of the axones during the early or incomplete stage of ischemia, with loss of pain and sensation resulting later when the nerve has lost its ability to conduct any impulse as a result of complete or protracted ischemia. Thus, the pain of intestinal cramps may be due to ischemia of the nerves in the intestinal wall caused by spasm or distention. If distention or spasm is prolonged, pain is apt to disappear because the ischemic nerve has lost its conductivity. Or, the pain of angina pectoris may be great during the earlier stages when ischemia of cardiac nerves is only partial, but often disappears after myocardial infarction occurs and occlusion of a coronary artery removes all blood supply to these nerves. My hypothesis for explaining the infrequency of typical cardiac pain in patients with hypertrophied hearts has been presented previously.[4] According to that study, the myocardial nerve fibers remain close to their capillary blood supply and so do not suffer ischemia proportional to that of the muscle fibers in cardiac hypertrophy. The muscle fibers enlarge with hypertrophy and push the capillaries, which do not multiply, farther apart than in the normal sized heart. Therefore, the muscle fibers are poorly nourished and function poorly, but the nerve fibers remained well supplied with blood and do not give rise to the painful sensations arising from ischemic nerves.

"Referred pain" is still poorly understood. Using the findings of this study, a reasonable hypothesis may be constructed to explain referred pain on the basis of ischemia of a peripheral nerve to skin or muscle. Such a nerve may become ischemic as a result of spasm of its vasa nervorum and cause painful sensations in its area of distribution. Such spasm may be induced by stimuli coming from the autonomic cell body groups in the central nervous system segment where the afferent nerve fibers from the injured visceral organ terminate. For example, "cardiac pain" in angina pectoris or myocardial infarction may be referred to the skin and muscle of the sternal, pectoral, or left arm regions, because the nerves to those areas become ischemic due to a reflex arc composed of the following components: (1) anoxia of a myocardial nerve stimulates (2) impulses along afferent cardiac nerves to (3) dorsal root ganglion cell bodies in the cervical segments and their central axones, terminating on (4) cell bodies in the dorsal part of the lateral horn of gray substance (the dorsolateral or intermediolateral groups of cells), which in turn, send (5) efferent sympathetic effector

axones via the white rami communicantes to the smooth muscle in the vasa nervorum of peripheral nerves distributed to the areas of "cardiac pain"; (6) spasm of these vasa nervorum produces ischemia of the nerve which causes impulses to go over the spinothalamic tracts from these peripheral nerves and results in consciousness of pain in the area supplied by these ischemic nerves (Fig. 8).

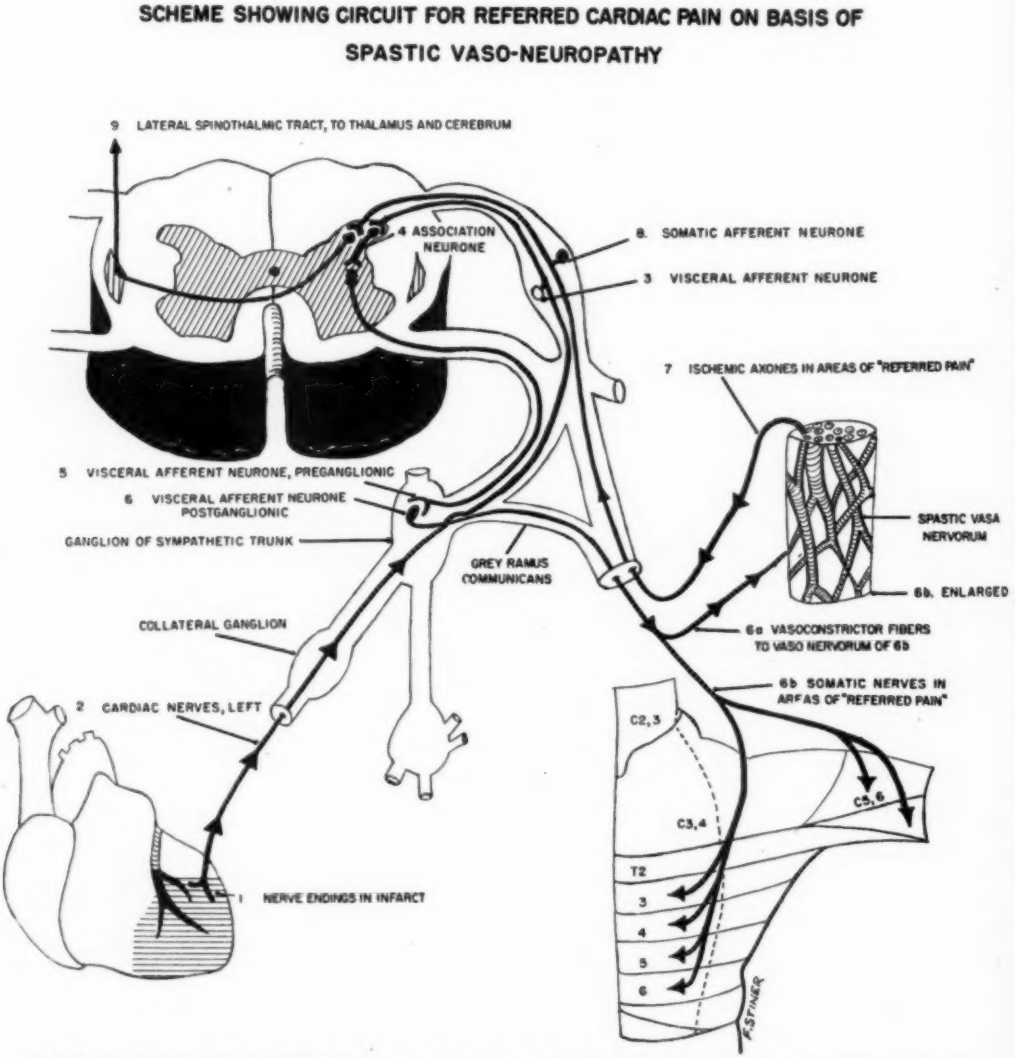

Fig. 8.—Reflex arc for "referred pain" on basis of vasospasm of vasa nervorum in peripheral nerves.

Information of therapeutic value to be derived from these studies is indirect. There is emphatic support of the need for careful manipulation of nerves during surgery with every effort being made to avoid (1) obstructing the blood

supply to nerves, (2) stripping of the epineurium, and (3) stretching or compressing nerves in any way. Inasmuch as ischemia of the nerve can result in its disintegration, efforts to prevent this may indicate at times the use of sympathetic nerve block and vasodilating or anticoagulant drugs.

It is probable that ischemia can prevent or hinder the regeneration of a nerve following injury by trauma, infection, or other cause. Experiments have been started to evaluate the role of the vasa nervorum in the regeneration of severed nerves. Likewise, the value of vasodilating drugs, anticoagulants, nutritional threapy, or sympathetic block needs to be evaluated as far as their effect upon the vasa nervorum is concerned. Initation of thrombotic, spastic, and proliferative vascular lesions can be tried by injecting ferric chloride, hyper-renin, or sodium morrhuate into the nutrient arteries of nerves.

The role, if any, of the vasa nervorum in many other disorders should be investigated. These disorders include hypertension, cardiac arrhythmias, varicose veins, nutritional deficiencies, pernicious anemia, diabetes mellitus, and referred pain. Patients with any of these conditions which decrease circulatory efficiency need to be cautioned against lowering the threshold for ischemia in any way. They must be taught to avoid crossing their legs, sitting improperly, sleeping on their arms or with the limbs compressed and angulated in any way, or wearing any constricting clothing or dressings. Tobacco should be avoided, especially by patients with neuropathy of any type, because the superimposed vasospasm may make the neural ischemia complete and irreversible.

CONCLUSIONS

1. The blood supply of nerves has been shown to be very abundant. The smallest nerve has an adequate blood supply.

2. This blood supply was obliterated by ligating nutrient arteries of a nerve, by stripping off the epineurium, by compressing a nerve or stretching it, and by injecting embolic substances into a nutrient artery. Having produced ischemia of the nerve by these methods, it was studied by injecting dye through the aorta into the vasa nervorum, and was found to alter the function and structure of the nerve.

3. Peripheral nerves of man may be made ischemic by similar processes and by proliferative, vasospastic, or thromboembolic vascular diseases affecting either arterial or venous blood supply of the nerves in a great variety of clinical conditions (for example, diabetes mellitus, thromboangiitis obliterans, arteriosclerosis, arterial embolism and thrombosis, phlebothrombosis, stretching or compression of nerves, anemia, or hemoconcentration). Sensory and motor changes were closely correlated with ischemia of nerves in the cases studied by injecting dye or by sections.

4. Crossing the legs, sleeping or sitting in a position that causes compression or stretching of nerves, and the use of constricting clothing or vasospastic drugs like tobacco should be avoided by patients with ischemia of limbs. Tingling, numbness, and similar mild complaints may indicate early stages of ischemic

neuropathy and may, therefore, be signs of serious import. Benefit may follow vasodilatation and correction of causal factors.

5. A "reflex arc" for explaining "referred pain" on the basis of neural ischemia is proposed.

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EXPERIENCE WITH THREE VASCULAR FRAGILITY TESTS IN HYPERTENSION

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FOR many years clinicians have noted hemorrhagic tendencies in a certain percentage of their hypertensive patients. Although abnormal vascular fragility represents a clinical condition of obscure and multiple etiology, new interest has been aroused in the field by the introduction of new agents reported to have possible favorable effects in abnormal capillary fragility.[1-4] Most investigators have used one of several different tests to determine abnormal fragility, all based on the number of hemorrhages counted in a specific area following the application of suction or a constricting band.

METHODS

A number of methods have been devised for measuring capillary fragility. These may rightly be divided under two major headings:

1. The negative pressure method, developed by Hecht,[5] da Silva-Mello,[6] Dalldorf,[7] and others.
2. The positive pressure method, based on the work of Leede,[8] Göthlin,[9] Beaser and associates,[10] and others.

The negative pressure method measures the frequency of capillary rupture or diathesis at graded levels of negative pressure over a selected time period. The end point or critical pressure varies according to the criteria selected.

The positive pressure method consists of the application of a constricting band, such as a blood pressure cuff, at a definite pressure, and counting the number of petechiae occurring during a given time period.

The results of one investigator are difficult to compare with those of another because of variations in criteria, technique, and interpretation of results.

In this particular study, we have tried to compare three different methods which were used simultaneously:

1. The Göthlin Test,[9] a positive pressure method in which a blood pressure cuff is inflated to 35 mm. Hg for fifteen minutes, and to 50 mm. Hg for fifteen additional minutes. The number of petechiae is counted in a 6 mm. circle in the antecubital fossa.

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Presented at the Twentieth Scientific Meeting of the American Heart Association, Atlantic City, N. J., June 6 and 7, 1947.

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2. The negative pressure test, using an apparatus designed by Dr. Carl Johnson.[12] A suction cup 1.0 cm. in diameter is placed on the antecubital fossa for thirty seconds, and moved to a contiguous area for each reading. The number of petechiae is counted at pressure levels ranging from 100 to 700 mm. Hg, rather than selecting the appearance of 1 to 3 petechiae as the end point (see Chart 1).
3. A cuff trauma test of our own, in which a blood pressure cuff is inflated three successive times from 0 to 300 mm. Hg and allowed to return to 0 slowly, as in taking a blood pressure. The area under the cuff and distal to the cuff is observed for petechiae and the frequency graded 1 to 4. Grade 1 represents a few petechiae under the cuff; Grade 4 a mass of petechiae down the forearm and onto the dorsum of the hand.

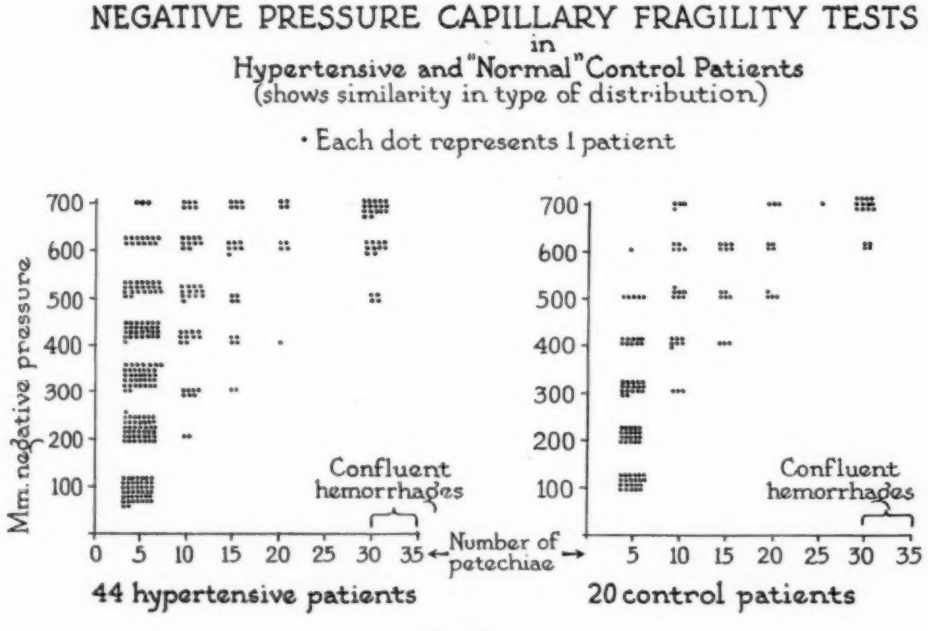

Chart 1.

We have classified the patient as having increased capillary fragility:

1. If more than six petechiae are present after the first step of the Göthlin Test.
2. If a total of thirty or more petechiae are present at successive 100 mm. readings between 100 and 500 mm. Hg of negative pressure.
3. If a shower of petechiae are found under the cuff or distal to the cuff following inflation to 300 mm. Hg three successive times.

Our interest in rupture of the vessels of the skin and subcutaneous tissues dates back to the days when venesection was commonly employed in patients with hypertension who had suffered a cerebral vascular accident or left ventricular

heart failure. The occasional patient would show a shower of coalescing masses of petechiae in the extremity from which the blood was taken. A more prolonged application of the constrictor during the procedure occasionally resulted in massive areas of petechiae, which instantly became ecchymotic and disfigured the arm for ten to twenty days. It was our impression at that time that the appearance of such degrees of petechiae meant severe vascular disease in these hypertensive patients.

During the past twenty years of special interest in vascular disease, the periodic appearance of numerous hemorrhages under and below the blood pressure cuff of the hypertensive patient has been recorded. This phenomena of the rupture of the small vessels of the arm during the course of taking a blood pressure appeared often enough to cause us to standardize our technique, and for want of a better name, we have called it the "cuff test." After taking the blood pressure in a routine manner three separate times in order to establish the patient's basal level, we inflate the cuff until the column of mercury rises to 300 mm. three times, deflating the cuff completely and flexing the arm each time, after which the presence or absence of petechiae are noted. All members of our hypertensive clinic, as well as medical students, have learned to observe and grade the presence or absence of petechiae following this simple procedure. If no petechiae appear, the cuff test is reported as zero. If petechiae appear under the cuff but along the wrinkles only, it is considered Grade 1. If petechiae appear within other areas under the cuff, but not below the cuff, it is Grade 2. Petechiae appearing both under the cuff and under the antecubital fossa are Grade 3, and Grade 4 is recorded when the petechiae appear down the forearm or onto the dorsum of the hand.

These observations have demonstrated that: (1) The cuff test is usually negative in patients with hypertension. (2) Patients with a positive cuff test show wide variations in the degree of fragility from month to month, regardless of treatment. (3) Positive cuff tests were most often related to the severity of the disease, especially when the diastolic blood pressure is high. (4) The appearance of petechiae coincided with vascular crisis of hypertensive encephalopathy, retinopathy, nephropathy, or other vascular episodes. Such observations over several years have caused us to look upon the presence of a positive cuff test as a finding of real clinical interest, if not a warning of impending danger when it is Grade 3 or more.

However, many unexplained factors seem to cloud our interpretation. For instance, the tests seemed to be much more frequently positive in women. Second, a positive cuff test might occur in patients who had no hypertension or other evidence of systemic vascular disease. Third, patients with advanced nephritis and complicating hemorrhagic phenomena, such as vascular bleeding in the eye grounds, gastrointestinal, and respiratory tracts, or deep ecchymotic areas in the subcutaneous tissue, would often have a negative cuff test.

Recently, our interest has again been aroused by the introduction of new agents reported to have a favorable effect on hemorrhagic tendencies by increasing capillary resistance so that we have again given critical evaluation to a group

of hypertensive patients, both from a standpoint of methods of measuring increased capillary fragility and the effect of these newer agents on this fragility.

MATERIAL

We have studied a group of forty-four unselected new patients with hypertension as they entered the renal vascular clinic of the Northwestern Medical School. These patients comprise a random sample with a similar socioeconomic background without regard to disease severity or any other specific factor except that they had hypertension. Fragility tests were repeated once or twice weekly on all patients showing any evidence of increased vascular fragility, while those showing no abnormality and severity controls were tested once or twice each month.

Before presenting the results of our studies of capillary fragility in patients with hypertension, the following information is offered in so far as it affects the evaluation of any study of capillary fragility. Reported studies in twenty "normal" controls aided us in selecting what we considered to be the most suitable criteria and pitfalls involved in correctly interpreting our data.

1. The reliability of the Göthlin Test is in the variety of 0.90 (maximum 1.0) when negative tests alone are considered. As the test becomes progressively more positive, the reliability dimininshes to .05 or below, when the number of petechiae range above 12 to 15.

2. Skin temperature has a pronounced effect on capillary fragility. Heat applied for two or three minutes to the forearm markedly increases capillary fragility. Likewise, fragility will decrease following the application of cold to the same area.

3. When positive or negative pressures are used as a measure of fragility, it is to be remembered that the weakest capillaries are being ruptured and tests which measure only a small portion of a large capillary population are subject to wide variations and follow a different type of distribution.

4. Skin thickness: Blondes, who are more likely to be thin-skined, have a greater tendency to increased fragility than brunettes. Similarly, hirsutism strengthens capillary tone.

5. Other factors, such as tissue anoxia and the nutritional state of the individual, particularly as it applies to avitaminosis, complicate the interpretation of the test.

6. Endocrine factors definitely influence the susceptibility to capillary rupture. Brewer[13] has shown that this susceptibility is greater premenstrually than at any other period during the menstrual cycle. He also demonstrated that adrenalin produces the same tendency in man. It is possible that both adrenalin and the adrenocortical hormone influence the ease of capillary rupture.

It is well known that women in menopause have a tendency toward formation of spontaneous ecchymotic-type hemorrhages. We have found that this is often associated with a positive cuff test and a marked increase in the Göthlin

index, even though there is no other evidence of vascular disease. Both the ecchymotic tendency and the capillary fragility will become more normal following adequate estrogenic substitution therapy, but are not affected by rutin or Vitamin C. This is well illustrated by the following case:

CASE 1.—Miss L. B., 45 years of age, came to the clinic complaining of the usual menopausal symptoms; hot flashes, increasing irritability, insomnia, and diminution of menstral flow. In addition, she complained of numerous bruises on her legs, thighs, and arms which were in no way related to trauma. When the blood pressure was taken in the routine manner, showers of petechiae appeared beneath the cuff and down the forearm to the dorsum of the hand (4 + cuff test). The blood pressure averaged 145/85. The Göthlin index was 60. There was no evidence of blood dyscrasia and the prothrombin and bleeding times were normal. Rutin, administered in daily doses of 180 to 200 units for six weeks, had no effect on either capillary fragility or ecchymosis. Vitamin C, calcium, and sedation were also of no avail. Thereafter, estrogenic therapy was started and within fourteen days all positive tests of her abnormal vascular fragility as well as the areas of ecchymosis had disappeared. There has been no recurrence during the past ten months, during which time she has received an estrogenic substance.

7. Leonard Keeler,[14] the well-known criminologist, in a personal communication has stated that the blood pressure cuff on the polygraph causes showers of petechiae to occur in a large number of subjects regardless of age, economic status, or blood pressure, although he reports a preponderance of increased fragility in women subjects.

8. We have previously mentioned that patients with advanced renal disease who have evidence of spontaneous hemorrhages elsewhere in the body, have normal cuff tests and Göthlin indices. This same fact obtains in patients with cirrhosis of the liver. These patients who show spider nevi, dilated abdominal veins, and esophageal varices, and who have nutritional abnormalities of the skin and body tissues, should be expected to show marked increase in their capillary fragility as measured by the positive or negative pressure techniques. However, capillary fragility is more often than not normal in spite of the fact that there are often gross changes in the prothrombin time, blood protein, blood cholesterol, and vitamins C and K.

9. Four of twenty control patients (20 per cent), free from cardiovascular disease but selected from the same socioeconomic status, revealed abnormal fragility. We also noted that repeated tests of the hypertensive group shows fluctuations which would change the category of the patient from borderline to normal.

A critical review of the results obtained in the hypertensive group, the control group, and in our pilot experiments leads us to doubt that repeated simultaneous use of the three tests adequately fulfills the need for a quantitative test of increased fragility. Even though a more accurate test should be developed that would measure more precisely the fragility of superficial skin capillaries, we would still be unable to draw any conclusions concerning the status of the capillaries anywhere but in the superficial layers of the skin. Factors which control vascular bleeding in the subcutaneous tissues and in the organ systems themselves cannot be measured by this type of test. Bearing these limitations in mind, the following results were obtained in a series of forty-four unselected patients with hypertension.

RESULTS

		NUMBER	PER CENT
1	Hypertensive patients examined	44	
2	Patients with increased fragility according to the Göthlin Test Index	7	15.9
3	Patients with 30 or more petechiae between 100-500 mm. of negative pressure	7	15.9
4	Patients showing petechiae following 300 mm. cuff trauma test	11	25
5	Patients treated with potassium thiocyanate	22	50
6	Thiocyanate treated patients manifesting increased fragility	3	13.6

It can be seen from this tabulation that the increase of capillary fragility occurs in approximately 16 per cent of the hypertensive patients, both as measured by the Göthlin index and the negative pressure techniques. Although the cuff test is a much more rapid technique for measuring capillary fragility, it is not as accurate a measurement as the other tests.

In our series, 25 per cent of the hypertensive patients showed abnormal fragility by the cuff test. Griffith[15] reported an incidence of 21 per cent increased fragility in 1,219 hypertensive patients. Our figures are quite similar to his. However, we must not forget that a certain percentage of normal individuals free from cardiovascular disease may also show increased capillary fragility as measured by both positive and negative techniques. In our group of control patients, 20 per cent showed increased capillary fragility.

Several authors have made the statement that patients undergoing thiocyanate therapy are likely to have abnormal capillary fragility. Shanno[16] stated that eleven of his series of twenty-four cases undergoing thiocyanate therapy revealed this tendency. Zfass[17] mentioned a favorable response of two cyanate-treated patients when given rutin in conjunction with thiocyanate. Griffith and Lindauer[18] have also alluded to the possibility that potassium thiocyanate may increase capillary fragility. The incidence of decreased capillary resistance of hypertensive patients on cyanate therapy was 13.6 per cent, which is approximately the same incidence as that of the hypertensive group.

Contrary to the opinion of other observers, we feel that a strongly positive cuff test or a high Göthlin index in the presence of a severe hypertension probably means advanced vascular damage, provided that the patient is not in the menopause. For many years we have noted that capillary fragility will improve as the blood pressure is reduced. We have also found that cyanate therapy with a subsequent drop in blood pressure improves vascular tone rather than increases capillary fragility. The following case illustrates the effect of cyanate therapy and a subsequent reduction of blood pressure in a patient with severe vascular disease and a marked increase in capillary fragility.

CASE 2.—Mrs. H. L., white, 47 years of age, stated that a blood pressure of 190 was first recorded when she was 29 years of age. Seven years before she came under our care, she had been told that her blood pressure was 285, at which time she suffered vertigo and fainting spells. Thiocyanate was administered for "several months" in 1944 without effect and a thoracolumbar sympathectomy was done in two stages in June, 1945. Within four months after the extensive sympathectomy, the blood pressure was well above the capacity of the usual mercury instrument which records only 310 millimeters. The diastolic pressure was regularly recorded at 160 to 170 millimeters.

We first saw Mrs. H. L. in April, 1946, when her blood pressure was 310+/160. The skin of the arm and forearm broke out with a mass of fine petechial hemorrhages which coalesced into large areas while the blood pressure was being taken a second time. Because of the severity of the vascular rupture, the cuff was changed to the opposite side where another attempt to record the systolic pressure failed (310+/170) but the diastolic pressure was obtained. Again the peculiar fragility resulted in masses of ecchymosis down the forearm onto the dorsum of the hand to the fingers. Potassium thiocyanate was started and the record on May 13, 1946, when the blood thiocyanate had reached 6 mg. per cent, shows that lines of traumatic petechiae were found under the sphygmomanometer cuff, but none appeared on the skin of the antecubital space or forearm; the blood pressure was recorded at 226/130, 260/130, and 266/130. On June 15, 1947, no traumatic or other evidence of increased vascular fragility could be demonstrated; the blood pressure was 240/120, 220/120, and 220/120, and the blood cyanate was 100 mg. per cent.

Although this patient's blood pressure was unusually high, the sharp degree of vascular fragility, as indicated by the cuff test, was returned to a normal state after six weeks of controlled thiocyanate therapy. This favorable response to thiocyanate therapy is usually noted by the third or fourth week and a complete disappearance of abnormal cutaneous vascular fragility may be expected in four to six weeks.

An analysis of the individual cases manifesting increased fragility revealed several interesting conditions. Six of the seven patients showed evidence of advanced degenerative retinal changes and moderate to severe renal impairment, as shown by the presence of abnormal elements in the urine and poor renal function tests. Two of these patients submitted to thoracolumbar sympathectomies. The renal biopsies which were taken at the time of operation showed a diffuse arteriosclerosis as well as arteriolosclerosis. Three patients in this group gave a history of abnormal bleeding. Other associated disease conditions were: cardiovascular accident in one case, coronary thrombosis, detached retina, and Kimmelstiel-Wilson's syndrome. Here again we see that given a patient with advanced hypertension, the presence of abnormal capillary fragility probably means a severe generalized vascular involvement.

Rutin was administered in daily doses of 180 to 200 mg. to all patients showing abnormal fragility. Three of the seven patients continued to show borderline increased fragility during the two-month period of observation. One patient showed a temporary improvement during the first month, with a return to abnormal fragility during the second month in spite of continued treatment. In three cases capillary fragility returned to normal. No significant reduction in blood pressure was found in any of these patients. No signs of toxicity were noted. No other subjective or objective changes could be attributed to the drug. There was no change in the progress of the disease.

Our results compare favorably with those reported to us by Taylor and Page[19] of the Cleveland Clinic, who repeatedly performed the Rumpel-Leede test on forty patients with hypertensive vascular disease over a six-month period. Twenty-two of their patients were given 300 mg. of rutin daily. Eleven of these had a decreased number of petechiae during period of observation. The other eleven showed no improvement, and of this latter group, three had cerebral vascular accidents. One had a myocardial infarction while taking rutin. The remaining eighteen patients received no rutin. Fifty per cent of this group

likewise showed a definite improvement in capillary fragility while under observation for a six-month period without treatment. None of this group developed signs of acute vascular insufficiency. In an attempt to establish the value of estimates of capillary fragility among patients with hypertension, the Rumpel-Leede test was performed on several hundred normal persons and patients with various diseases. Acutely ill patients over 50 years of age often showed increased capillary fragility. This was particularly true of patients with a significant amount of arteriosclerosis and accompanying hypertension. The degree of capillary fragility varied from month to month in hypertensive or other patients. With the general improvement resulting from bed rest and recovery from heart failure, there were usually fewer petechiae produced by the test employed.

It was the opinion of the observers that in their hands rutin was of no benefit in the treatment of hypertension or its complications.

DISCUSSION

We do not believe that any of the three tests described adequately fulfills the need for an accurate quantitative method for determining increased capillary fragility and the response to therapy. They are all gross qualitative category tests, subject to spontaneous variation in the same patient from week to week. Many complex factors influence the susceptibility of capillaries to rupture, and these same factors render the interpretation of results more difficult.

In view of the lack of sensitivity of the capillary fragility tests, and the many factors influencing the determinations, one must be careful in interpreting the response to therapy in a group of individuals.

Although rutin has been efficacious in correcting abnormal capillary fragility in a large series of patients, our results in a small group have been disappointing. Glazko and associates[20] have recently described a fluorophotometric method of determining the blood levels and execretion of rutin and other members of the flavone group. A great deal of additional pharmacologic study must be done before we can assign to rutin a prominent role in the correction of a possible deficiency state.

The possibility that thiocyanates, of themselves, increase capillary fragility is a debatable point. Our results do not show that thiocyanates increase capillary fragility; in fact, the tendency to capillary rupture appears to decrease as the blood pressure is lowered by thiocyanates.

Abnormal capillary fragility seems to be associated with the presence of advanced, diffuse degenerative arteriosclerotic changes. Rutin does lessen the tendency to petechiae rupture in some cases, but the results in our small group series have been disappointing.

SUMMARY

The efficacy of three tests used in measuring capillary fragility in patients with hypertension has been reported. A cuff trauma test, although less accurate than either the Göthlin index or negative pressure test, is rapid, simple to perform, and gives an excellent preliminary estimation of the severity of the vascular dis-

ease of the hypertensive patient. In addition, it is a guide to the degree of clinical improvement of patients undergoing cyanate therapy. The Göthlin index, although showing less variability than the negative pressure test, is probably not as sensitive as the latter. In doing the negative pressure test according to the technique as first described by Johnson, we do not believe that individual readings of the negative pressure at which the first petechiae appear in a small localized area are reliable criteria. For this reason, we prefer to do serial counts at 100 mm. gradations, from 100 to 700 mm. Hg, and count the total number appearing between 100 and 500 mm. of mercury. The most consistent results were found by this method.

Of forty-four hypertensive patients examined by three capillary fragility tests, approximately 16 per cent had increased fragility as measured by the Göthlin index and negative pressure technique. Twenty-five per cent had increased fragility following the cuff trauma test. Only 13 per cent of the cyanate-treated patients manifested increased fragility, while 20 per cent of our normal control patients showed increased fragility.

Even though it is our clinical impression that patients with a severe degree of hypertension who manifest a marked increase in capillary fragility as measured by the Göthlin index or cuff trauma test have widespread vascular disease, we cannot interpret, on a scientific basis, the condition of the generalized vascular bed in the cerebral, cardiac, or renal systems on the basis of studies of superficial capillary fragility.

Multiple extrinsic causes of capillary fragility aside from vascular disease must be considered before any interpretation can be made. Normal individuals without hypertension or end artery disease may show abnormal capillary fragility as measured by these tests. Likewise, patients with advanced degrees of generalized vascular damage may have normal capillary fragility. The degree of capillary fragility in any one individual is not consistent but varies from month to month.

CONCLUSION

1. Three capillary fragility tests, the Göthlin Test, the negative pressure test, and the cuff trauma test, have been compared and evaluated.

2. It does not appear as though any one of these tests adequately fulfills the need for an accurate quantitative test.

3. Abnormal capillary fragility was found in 15.9 per cent of forty-four hypertensive patients.

4. Thiocyanates did not increase capillary fragility in this particular series.

5. Rutin, administered in 180 mg. doses daily, reduced the susceptibility to capillary hemorrhage in three patients. In three, the results were questionable.

6. Abnormal capillary fragility was associated with advanced diffuse degenerative arteriosclerosis in most of our cases.

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NIGHT CRAMPS IN HUMAN EXTREMITIES

A Clinical Study of the Physiologic Action of Quinine and Prostigmine Upon the Spontaneous Contractions of Resting Muscles

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IN OCTOBER, 1940, we reported the successful management of "night cramps" with quinine sulfate[1] and stated that further investigation relating to the mechanism of action was being pursued. Many additional patients were treated from that time until government regulations restricted the use of quinine for general use. Twenty patients of this new series were followed in the Vascular Disease Clinic of the Cincinnati General Hospital over a protracted period for the purpose of investigating both the site of action of the drug and the physiologic factors responsible for the onset of the cramps. Because of the preclusion of the general use of quinine during the last few years, this report dealing with the pharmacologic and physiologic implications of the study has been withheld until the present.

MATERIAL

In contrast to the first group, which was selected from patients already attending the Vascular Disease Clinic for other conditions, the patients used in this study were referred by other clinics specifically for the care of "night cramps." Concomitant disease entities were to be expected. Most of these were coincidental. Some definite correlation, however, was established with certain disease entities. Fifty per cent of these patients were referred to us by the Diabetic Clinic. Twenty-five per cent of the patients were being treated for varicose veins of the legs or gave a history of having had varicosities. Consistent with the association of cramps and varicosities in this last group was the finding of a history of peripheral venous thrombosis or thrombophlebitis in many of our private patients who had night cramps. The incidence of arterial disease in these patients was high, but special vascular studies on ten of them showed serious arterial deficiency in only four. Avitaminosis, as evidenced by paresthesias of the extremities, was common, particularly in the older patients. Vitamin B complex deficiencies are frequently a cause of night pain and numbness

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Presented at the Twentieth Scientific Meeting of the American Heart Association, Atlantic City, N. J., June 6 and 7, 1947.

in the distal portion of the extremities. Proved cases of vitamin deficiencies referred to our clinic by error and relieved by vitamin therapy were excluded from this study. In those in whom night cramps and avitaminosis coexisted, the muscle cramps were relieved first by quinine before instituting vitamin therapy, or thiamine chloride and yeast were administered initially and continued while the quinine and placebo capsules were alternated. In no instance did vitamin therapy relieve the muscle cramps.

METHOD, DOSAGE, AND RESULTS

The reports of Wolf and Kennedy[2a,b] regarding the antagonistic effect of quinine hydrochloride and prostigmine salts upon myotonia and myasthenia gravis prompted our original trial of quinine sulfate for the relief of night cramps. It seemed important, therefore, to recheck not only the beneficial effect of quinine salts but also the action of prostigmine upon patients susceptible to these night cramps. Quinine sulfate, 3 grains (0.2 Gm.), a placebo, and prostigmine bromide, 7.5 or 15.0 mg. were prepared in identical capsules. Patients were started with either the placebo or quinine sulfate originally; if the latter, the placebo was substituted as soon as relief of the night cramps was noted. Three grains of quinine sulfate were experimentally established as the initial therapeutic dose and administered after each meal. The morning dose was of little benefit, except to those experiencing muscle cramps while resting during the day. Three grains of quinine at bedtime were sufficient in some instances; two grains were insufficient for most patients. Faster acting quinine dihydrochloride was given some patients at bedtime where cramps appeared promptly upon retiring. Later, three grains of quinine sulfate after supper supplemented by a similar dose at bedtime proved equally beneficial. Relief was usually obtained on the first or second night. Often it was complete at once; sometimes milder or less frequent cramps persisted for some days after treatment was begun. Repeated alternations with placebo capsules over long periods were possible in many patients. Eventually, after a varying degree of quinine therapy, release of muscle cramps persisted without medication. Whether this was due to the interruption of some metabolic cycle by quinine or to the natural history of the condition could not be established. Night cramps are usually periodic regardless of treatment. Relief, however, was so prompt in all cases and pain recurred so often with placebo capsules that there could be no question as to the specific action of the drug in this condition.

In those patients who came to the clinic complaining of night cramps and who received prostigmine bromide before the quinine, no alteration in the frequency or intensity of the cramps was acknowledged by any of the patients. One patient who was able to precipitate spasm of the muscles of the leg by forcefully extending his foot for twenty-five seconds received two ampules of prostigmine methylsulfate (1:2000) without influencing the time of onset of the cramps or the ability to obtain relief from them by pressing his foot upon the floor. Tests were made every five minutes from twenty to forty-five minutes after subcutaneous injection of the prostigmine. In only two patients did prostigmine bromide

induce muscle cramps after they had been relieved by quinine. This may have been coincidental since quinine gave relief despite continued administration of prostigmine in these patients and since prostigmine alone, upon discontinuance of quinine sulfate, failed to precipitate spasm.

Other Effects of Prostigmine.—It is possible that larger doses of prostigmine might have increased the night cramps. The dosage used, however, was adequate to produce other physiologic effects of prostigmine, the most interesting of which was peripheral vasodilatation. Patients with peripheral arteriosclerosis, while reporting no change in muscle spasms at rest, volunteered the information that their extremity "no longer felt cold," or that "the heaviness" had left, or that "life was back" in a toe which had been numb. Spontaneous burning pains often were abated or were reduced in intensity. One patient in his late forties noted marked improvement in intermittent claudication. The other patients with intermittent claudication were older and obtained little or no relief of muscle cramps on exertion. Perlow[3a,b] also reported that intermittent claudication in arteriosclerotic patients was most refractory to prostigmine therapy.

Another effect of prostigmine was its action on joints with hypertrophic arthritis. Patients called our attention to increased motion in an ankle joint which had been restricted for years, or reported increased mobility in knees or feet. Subsequently, we have used prostigmine in a selected group of patients who were suffering from osteoarthritis and we have noted improvement in many of them. Trommer and associates[4a,b] recently reported thirteen patients with rheumatoid arthritis who showed marked and prompt relief after the use of prostigmine. Our series was restricted to patients with hypertrophic arthritis and we noted beneficial response with relief of pain and stiffness of the joints within twenty to thirty minutes of the subcutaneous injection of prostigmine methylsulfate. The action may be one of relaxation of periarticular tissues through vasodilatation similar to that produced by short wave diathermy treatments, rather than relief from spasm by the action of prostigmine within the spinal cord, as described by Kabat and Knapp.[5]

Reports of uncomplicated cases with night cramps were published in our preliminary report. This additional history is added to show the existence of concomitant disease as well as to evaluate the action of prostigmine.

B. F., a Negro woman 60 years of age, came to the Vascular Disease Clinic on May 1, 1941, complaining of "night cramps." Her sleep had been disturbed for months by spasms in the calf muscles of the legs. The spasms were more pronounced following unusual activity during the day. In addition, she gave a history of adequately treated syphilis, diabetes mellitus which was controlled by dietary management alone, and arteriosclerotic heart disease in a state of compensation with digitalis therapy.

Physical examination revealed an alert woman who appeared much older than 60 years. In addition to generalized arteriosclerosis and hypertrophic arthritis, she had a smooth beefy-red tongue and complained that her feet "burned." Oscillometric tracings showed diminished pulsation in both legs. It was decided to postpone treatment for the vitamin deficiency until after the night cramps had been relieved.

Quinine sulfate, 3 grains, was prescribed after dinner and at bedtime. Two weeks later, she reported complete relief of the night cramps. This relief started on the day after quinine was

first given. Quinine sulfate was continued and, to combat the vitamin deficiency, thiamine chloride, 15 mg. together with an ounce of dried brewer's yeast, was given daily.

During the next six weeks there was much improvement in the vitamin deficiency. The dose of thiamine and yeast was thereafter kept constant and quinine sulfate therapy alternated with a placebo and prostigmine. On July 28, she reported severe night cramps following the substitution of the placebo capsule for the quinine. Quinine sulfate was again administered for one month, and by August 20, only one muscle cramp had occurred. On September 17, no night cramps were reported despite the fact that quinine sulfate had been discontinued two weeks before. This persistent relief following the discontinuation of the drug is a typical clinical effect of varied periods of quinine administration in patients with night cramps. At this time prostigmine bromide was substituted for the quinine. On September 24, no cramps had appeared following prostigmine bromide, 7.5 mg. after dinner and at bedtime. Prostigmine bromide, 15 mg. three times a day, was administered. On October 22, no cramps had been noted. The patient reported slight weakness and sweating following the use of "these capsules." The dose of prostigmine was then reduced to 7.5 mg. three times a day. On October 29, the patient reported only one slight night cramp. She volunteered the information that movement of her "stiff joints" was freer. Prostigmine was administered for more than a month with no return of the night cramps. Vitamins were administered throughout this period. During the month of December, only the yeast and thiamine were administered. In January, she reported no return of night cramps but her joints again "became stiff" following the discontinuance of prostigmine.

DISCUSSION

The theory of the chemical transmission of nerve impulses assumes the discharge of choline from nerve endings, which in turn stimulates the motor endplates in the muscle. The choline is promptly destroyed by the cholinesterase in the blood. Physostigmine and prostigmine protect the choline against destruction by this enzyme. They thus amplify or prolong the choline effect upon the muscle endplates. Quinine supposedly diminishes the sensitivity of the endplates to the stimulation of the cholinergic nerves. Notwithstanding the clinical value of this hypothesis, most investigators believe that further experimental work is necessary to establish accurately the mode and the site of the action of prostigmine and quinine. Some doubt is added by the fact that acetylcholine and acetyl-beta-methylcholine, the activity of which is protected by prostigmine, will not influence either myasthenia gravis or the myotonias.[7]

We are most concerned with quinine in this work. Though quinine salts might well antagonize prostigmine in certain diseases, they need not necessarily act at the same point. Harvey[8] states "it is possible that the drug (quinine) exerts its influence upon both the neuromuscular junction and the muscle itself." The exact effect of quinine on isolated muscle has been shown by the nerve muscle preparation of Briscoe.[9] Briscoe found that the perfusion of the preparation with quinine did not decrease the amplitude of contraction as much as it decreased the ability of the muscle to maintain tension upon repeated rapid stimulation. Thus, a refractory stage was created in skeletal muscle approaching that of normal heart muscle. The action is not unlike that of quinidine sulfate. Briscoe's experiments did not determine whether the myoneural junction or the muscle itself was the site of action of the quinine. Briscoe, however, compared the action of quinine to mild degrees of curarization. If her analogy is correct, further light is thrown on the point by Langley. Noting the tonic effect on skeletal

muscle when touched by nicotine, Langley[10a] found "that this contraction is prevented by a sufficient quantity of curare; and that the action of both poisons is unaltered, in essential features, by degeneration of the nerve endings."

Our clinical observations with quinine point more toward direct action upon muscle. First, prostigmine failed to initiate or increase the frequency of muscle cramps. Second, the physiologic circumstances attending the onset of cramps seemed to be related to metabolic conditions within the muscle at the time of onset. It was pointed out earlier that 50 per cent of our patients were referred to us by the Diabetic Clinic and that the presence of vein pathology was the next most consistent finding. Most interesting was the coincidence of both intermittent claudication and night cramps in four patients. In all four of these patients, the muscle spasm at rest was completely relieved by quinine sulfate while the intermittent claudication on exertion remained unchanged. We believe that the muscle spasm in these patients resulted from the stimulation of the muscle by metabolites, which accumulated as a result of venous stasis or by the products of abnormal muscle metabolism such as is observed in patients with diabetes mellitus. The high incidence of muscle cramps in pregnant women might be associated with the increase of venous pressure in the legs and is consistent with the concept of an arteriovenous communication in the placenta. If we are correct in the assumption that metabolites stimulate the muscle and cause cramps, one should expect an increase in metabolic by-products following exercise. Almost every patient noticed that muscle cramps at night were most severe following unusual activity during the day. One woman reported that she had night cramps in the calf muscle of the legs when she worked the pedal of her sewing machine during the early evening. This finding is not inconsistent with Gootnick's[11] correlation of cramp and postural defect where muscular stress would necessitate increased metabolic activity. The phenomenon of spontaneous muscle contraction at rest following activity seemed so similar to rigor mortis that we investigated the onset of rigor in animals following death from air embolus or lethal doses of quinine. No differences were noted. Experiments on animals dying following violent exercise with and without previous quininization are being pursued.

CONCLUSIONS

1. Twenty patients suffering from nocturnal muscle cramps at rest were observed for a prolonged period of time.

2. Night cramps appear to result from the action of some end product of metabolism, as in diabetes, or from poor elimination of normal end products of muscle metabolism, as in patients with venous stasis due to varicose veins, pregnancy, or following deep venous occlusion.

3. Increased muscular activity favors the development of night cramps in the rest which follows such activity.

4. No etiological or therapeutic relationship exists between intermittent claudication and muscle cramps at rest.

5. Quinine sulfate has been found to give prompt relief of night cramps in extremities.

6. Evidence indicates that the action of quinine is directly on muscle, rather than on the myoneural junction.

7. Quinine sulfate produces a refractory period in skeletal muscle that is similar to the refractory period in heart muscle.

8. Prostigmine, the supposed pharmacologic antagnonist of quinine, failed to increase the intensity or frequency of night cramps when administered in doses sufficient to produce the vasodilating effect of the drug.

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THE RELATION BETWEEN ARTERIAL PRESSURE AND BLOOD FLOW IN THE FOOT

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THE relationships between blood flow and arterial pressure in man have never been clearly elucidated, primarily because a satisfactory technique for raising and lowering the arterial pressure in a part, without using either vasoconstrictor drugs or intense sympathetic stimulation, or causing venous congestion, has been lacking. Because of the large surface area in relation to its total mass, the foot presents itself as an ideal anatomic subject for studying the relation between arterial pressure and blood flow in the skin. The mean arterial pressure in the foot may be doubled by standing upright. Venous congestion may be avoided by emptying the foot of its venous blood by applying to the foot a pressure which exceeds the hydrostatic venous pressure, but is well below the arterial diastolic pressure, and thus does not impede the arterial inflow. On release of this pressure, blood flows into the foot under a tremendous pressure head which is unopposed on the venous side until the foot is filled. In this study, the blood flow with the subject in the supine and erect positions was measured by means of a foot plethysmograph.

METHOD

The normal subjects were medical students and ambulatory patients without evidence of vascular disease or hypertension. Observations were made on only one patient with vascular disease. The studies were done at various times during the day, and food intake was not restricted. The room temperature varied on different days between 24.0° and 26.5° centigrade.

The plethysmograph used in this study has already been described.[1] It was bolted to the end of a hand-operated tilt table in such a manner that it could comfortably accommodate the left foot. The opening for the foot in the plethysmograph was covered with a rubber membrane, in the center of which was cemented a rubber sock. The left foot was fitted into the rubber sock, the neck of which was sufficiently redundant to fit snugly around the ankle when the

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This work was supported by a grant from the Life Insurance Medical Research Fund.
Received for publication April 30, 1947.
*Student Fellow of Life Insurance Medical Research Fund.
†Fellow of Life Insurance Medical Research Fund.

plethysmograph was filled with water. In order to avoid trapping air around the foot in the rubber sock, the instrument was filled with water when the subject was in the erect posture, thus forcing out all the free air. Soft tissue paper was placed around the ankle at the point where the rubber made contact in order to obviate the formation of a dead space when the plethysmograph was put in different positions. The rubber membrane through which the foot entered the plethysmograph was made as rigid as possible by a felt pad backed by wood sections cut to fit the ankle. Care was taken to avoid constriction of the ankle at any point.

The plethysmographic method for determining blood flow measures the initial rapid increase in foot volume which results when a venous cuff placed on the leg just proximal to the plethysmograph is suddenly inflated to a level approximately equal to the diastolic pressure. The initial increase in foot volume was recorded on moving paper by kymograph pen resting on a Brodie bellows. It was found that a bellows with a volume capacity of 40 to 50 ml. was desirable to obtain easily measurable tracings. The bellows was calibrated by adding known amounts of water to the plethysmograph.

The water surrounding the foot was kept at the desired temperature for at least thirty minutes before the blood flow measurements were recorded. During this time the subject rested quietly in the recumbent position. The water in the plethysmograph was mixed by a small electric stirring unit.

The arterial pressure was recorded with a mercury manometer by the auscultatory method in the erect and supine positions. The arm was placed at heart level.

The foot was emptied with the subject in the supine and erect postures by air pressure suddenly applied to the interior of the water-filled plethysmograph from a large reservoir.* The pressure was kept on the foot from four to eight seconds, which proved to be long enough to empty the venous system; it was then released and the blood flow recording begun one second after the release. In the recumbent position, 50 mm. Hg of air pressure were used to empty the foot; in the erect position, 110 to 130 mm. Hg of pressure were used, depending on the subject's height. Care should be taken to have large bores in the stopcocks so that air pressure will equalize rapidly when it is introduced or released. Despite these precautions, the time required for the air to expand and escape from the plethysmograph completely is sufficiently long that a portion of the curve recorded one second after release of the air pressure is the result of air expansion and not blood flow. To correct for this artefact, it is necessary to stop the blood flow into the foot by an arterial tourniquet and then obtain curves after release of the air pressure from the plethysmograph. When the slope of this curve is subtracted from the first curve, the true blood flow, expressed in cubic centimeters of blood per minute per 100 c.c. of foot (Fig. 1), may be calculated.

The method we have described was the most convenient one devised for measuring blood flow in the erect posture, for measurements could be made

*This effectively empties the foot when the plethysmograph is filled with water. It is not effective if used as an air plethysmograph.

repeatedly during a short period of time. In order to be certain that the correction for the air pressure was a valid one, the procedure was done in such a way as to eliminate that factor. The subject was tilted into the head-down position and air pressure was applied to empty the foot; an arterial cuff was then inflated just proximal to the plethysmograph to a pressure of 300 mm. Hg, and the air pressure in the plethysmograph was released. The subject was then immediately tilted to the upright position, the arterial cuff released, and the flow of blood measured. The period of arterial occlusion did not exceed twelve to fifteen seconds, which avoided a significant amount of reactive hyperemia (Fig. 1).

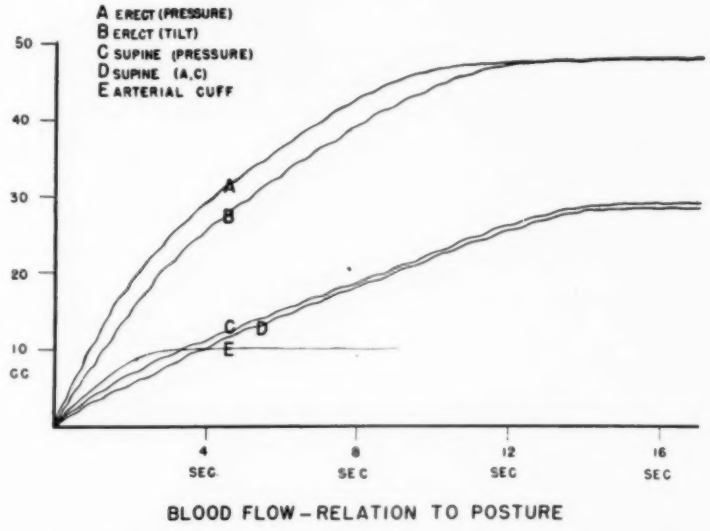

Fig. 1.—The blood flow into the emptied foot with the subject erect and recumbent (water temperature 45° C.). In this and subsequent diagrams, the ordinate is cubic centimeters and the abscissa is seconds. These figures were drawn to scale from the original tracings, with the exact time relationships indicated. The undulations in the blood flow lines indicate the arterial pulsations; they are absent in the tracings made with arterial cuff applied. Curves *A* and *C* were obtained after the foot was emptied by air pressure. Curve *E* is the curve of air expansion with the subject erect. Zero time on the graph is actually one second after the release of air pressure. *E* is subtracted from *A* to obtain the true blood flow. *B* is blood flow in the erect position, taken on release of arterial tourniquet which was applied immediately before tilting. The arterial inflow was occluded for fifteen seconds. *D* is the blood flow into the empty foot with the subject supine. The foot was emptied by air pressure and kept empty by the application of an arterial tourniquet. Fifteen seconds later the tourniquet was released and curve *D* inscribed.

Experiments were designed to determine what pressure would be required to empty the foot completely of its venous blood in the erect posture, and to determine the effect of the emptying pressure on the blood flow. A standpipe, 160 cm. in height, was fastened to the top of the plethysmograph and water was added to fill it to various heights between 110 and 135 cm., depending upon the height of the subject. The rubber tube connecting the plethysmograph to the Brodie bellows was then attached to the open top of this standpipe in such a manner that free communication existed from the interior of the plethysmograph to the bellows through the standpipe. Any change in the water level in the stand-

pipe immediately reflected itself in a rise or fall of the recording needle attached to the bellows. Blood flow determinations were then performed by suddenly applying the venous cuff, which encircled the ankle, at a pressure of 150 to 170 mm. of mercury.

The procedure for measuring blood flow during reactive hyperemia was similar to that which has been described many times.[2-4] The values given in the table represent the initial inflow into the foot occurring immediately after the release of the tourniquet.

Foot volume was measured directly by water displacement.

RESULTS

Maximum Dilatation of Vessels in the Foot.—It seemed desirable to measure the effect on blood flow of increasing the blood pressure in the foot with the vessels fully dilated as well as under more normal conditions. For that reason, observations were made to determine which procedures would produce maximal vasodilatation (Table I).

TABLE I. REACTIVE HYPEREMIA. RELATIONSHIP OF BLOOD FLOW (SUPINE) TO TIME OF ARTERIAL OCCLUSION

SUBJECT	BLOOD FLOW										
	32° C.				38° C.				45° C		
	TIME OF ARTERIAL OCCLUSION (MIN.)										
	0	5	10	15	0	5	10	15	0	5	10
B. F.	1.4	4.9			8.0		12.0		13.8		13.4
D. G.	3.0			12.2	8.4		17.6		22.0	22.4	
P. C.	3.2				8.0			15.0	12.0		
R. T.	4.7		5.2	7.2	6.3		9.2		17.3	17.5	
C. L.		6.5			12.0			17.0			
McD.			9.5	15.3				16.0	17.0		
L. M.	3.9	5.9		10.5				12.0	11.0		
G. B.		6.0		10.5	4.1				12.7		
G. B.	2.3			10.2	16.0		18.0		34.0	32.8	
J. W.	2.8			8.6	6.1		10.3		15.6		
H. D.	3.0			8.3					15.6	14.9	
J. B.	3.5		9.3						13.0		13.6
E. D.	4.2								14.3		
E. S.	4.0								13.5		
J. B.	3.5										
F. R.	1.9										
P. S.	5.3										
W. M.	7.8								11.3		
E. B.	7.6										
P. P.									17.4	17.8	

All figures expressed in c.c./min./100 c.c. of foot.

Fairly complete vasodilatation has been reported as occurring in the vessels of the forearm (a muscular area) after arterial occlusion with water surrounding the arm at 32° C. for a period of five minutes.[4] This is not true for the foot; the blood flow after arterial occlusion at 32° C. for five minutes was rarely more than 40 per cent of the maximal blood flow (Table 1). Arterial occlusion at 32° C. for fifteen minutes caused a further increase in the blood flow (on the average, about 70 per cent of maximal), but it rarely produced maximal blood flow. Arterial occlusion for ten minutes, with water temperature at 38° C., produced maximal blood flow in only one of five subjects (Fig. 2). Thirty minutes' immersion of

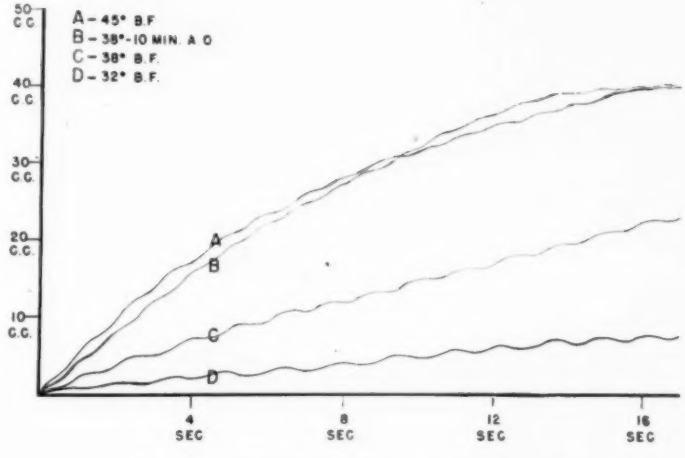

Fig. 2.—Increasing flow in the foot with increasing water temperatures. In this subject the blood flow (reactive hyperemia) at 38° C., following ten minutes arterial occlusion, is approximately equal to the blood flow at 45° centigrade. These flows were taken with the patient supine.

the foot in water at 45° C., which was as hot as the average patient could comfortably tolerate, produced maximal vasodilatation in almost 100 per cent of the subjects, as indicated by the fact that arterial occlusion produced no further increase in blood flow (Fig. 2). This had previously been demonstrated by Kunkel and Stead.[5] There is a large variety of stimuli capable of varying the blood flow at almost any water temperature; particularly anxiety, room temperature, or discomfort. It is important, therefore, to make an effort to keep the patient as comfortable as possible and not to allow the room temperature to vary widely. It is unwise to assume that local heat has caused maximal dilatation in the foot within the the plethysmograph until the other foot has become warm from reflex vasodilation.

Effect of Emptying the Foot of Its Venous Blood With the Patient Recumbent.—When the foot is placed in the plethysmograph, varying degrees of venous congestion occur because of the pad and form around the entrance, even though an attempt is made to avoid this. The blood flow in the foot emptied of its venous

blood is faster than in the full foot at both water temperatures of 32° C. and 45° C. (Table II).

TABLE II. BLOOD FLOW IN SUPINE POSITION

SUBJECT	32° C.		45° C.	
	FOOT NOT EMPTIED	FOOT EMPTIED	FOOT NOT EMPTIED	FOOT EMPTIED
W. B.	2.6	3.7		
W. M.	7.8	8.6	11.3	14.7
E. S.	4.0	4.8	13.5	17.5
J. B.	3.5	4.9	7.5	13.8
L. C.			2.1 (40°)*	3.6 (40°)
E. D.	4.2	5.6	14.3	19.0
P. S.	5.3	5.6		
F. R.	2.3	3.5		

All figures expressed in c.c./min./100 c.c. of foot.
*See text.

In those subjects in whom the blood flow was compared in the full and empty foot in the supine position, the following results were obtained:

The blood flows at 32° C. in the unemptied foot varied between 2.3 and 7.8 c.c. per minute per 100 c.c. of foot and between 3.5 and 8.6 c.c. in the emptied foot.

At 45° C., the blood flows in the unemptied foot varied between 7.5 and 14.3 c.c. per minute per 100 c.c. of foot and between 13.8 and 19.0 c.c. in the emptied foot.

The percentage difference at 32° C. is very nearly equal to that at 45° C., the average increases in blood flow from the full to the empty foot equalling 35 per cent and 39 per cent, respectively. The absolute difference in cubic centimeters at 32° C. is, of course, much smaller than at 45° centigrade. In comparing the blood flows in the supine and erect postures, it is advisable to compare the values for the emptied foot in both circumstances, for this obviates much of the variation in flow which occurs in the full foot (Fig. 3). The values for supine blood flows obtained at the beginning of this study were measured in feet which were not emptied, but the differences between supine and erect blood flows were of such magnitude that legitimate comparisons can still be made easily. (Those subjects in whom the foot was emptied are marked by an asterisk in Table III.)

Effect on Blood Flow of Increasing the Arterial Pressure in the Foot by Standing (Table III).—The mean arterial pressure in the recumbent position was calculated from the arithmetic mean of the values for the systolic and diastolic pressures. This value is somewhat higher than the true mean pressures. The mean pressure in the erect position was obtained by adding to the mean pressure calculated from the value obtained by the auscultatory technique the pressure of a column of water extending from the mean immersion level of the foot to the fourth rib. As the arch of the aorta extends higher than the fourth rib, the estimated pressure is probably somewhat too low. The estimated mean pressure

TABLE III. BLOOD FLOW IN C.C PER MINUTE PER 100 C.C OF FOOT

SUBJECT	AGE	32° C.			38° C.			45° C.			MEAN PRESSURE IN MM. HG	
		SUPINE	ERECT	STANDPIPE	SUPINE	ERECT	STANDPIPE	SUPINE	ERECT	STANDPIPE	SUPINE	ERECT
B. F.	30	1.4	13.7					13.8	31.0		95	190
P. C.	23	3.2	33.0					9.6	38.0		103	183
H. D.	30	3.0	8.3					15.6	36.0		89	169
B. P.	30	1.6	5.0	1.3							112	205
J. B.	28	3.5*	12.0					13.0	24.0		95	197
E. D.	22	5.6*	13.0	4.5				19.0*	48.0	17.8	80	180
E. S.	37	4.8*	9.5	4.0				17.5*	40.0	10.1	90	208
J. B.	22	5.0*	12.0					14.7*	47.0		94	192
F. R.	30	3.5*	9.0								96	187
P. S.	26	5.6*	12.2								88	184
W. M.	23	8.6*	17.0	6.6							91	198
E. B.†	30	15.0*	39.0								84	192
D. G.	28				8.4	33.0		22.0	44.0	21.5	108	206
R. T.	21				7.3	20.0					97	205
C. B.	27				12.0	35.0					90	191
G. B.	33				16.0	48.0		34.0	77.0	29.0	89	192
P. P.	24							17.4	55.0		77	178
L. C.	53				2.7* (40°)	9.6 (40°)	2.6				128	215

*Subjects in whom foot was emptied.
†Water temperature was at 35° centrigrade.

in the foot, with the subject in the upright position, was approximately double the estimated mean pressure with the subject in the supine position (Table III).

The blood flows at 32° C. in the erect posture ranged from 5.0 to 33.0 c.c. per minute per 100 c.c. of foot. In comparing the blood flow in the erect and supine positions, only values were used where the foot had been previously emptied of blood by air pressure before the arterial inflow was recorded. The increases in blood flow in the foot at 32° C. which resulted when the subject was changed from the supine to the erect posture ranged between two and three times the original level in the supine posture. The average increase was 2.4 times the original resting blood flow in the supine position.

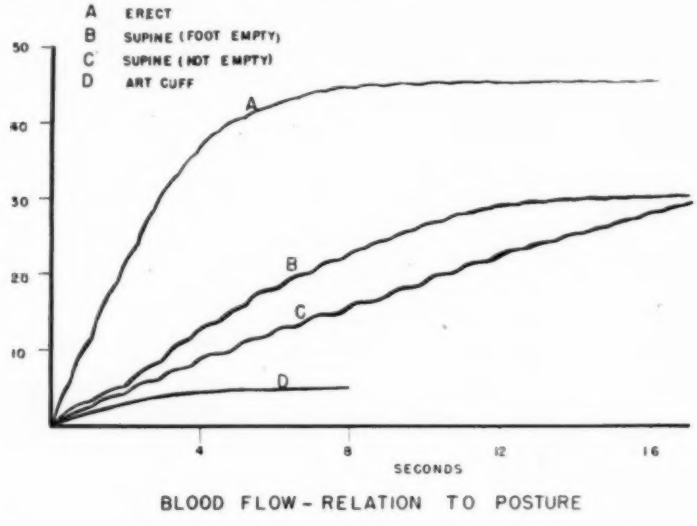

Fig. 3.—Blood flow into an unemptied and an emptied foot with subject recumbent compared with blood flow in emptied foot with subject erect. (Water temperature 45° centigrade.) *D* represents the curve of expansion of air occurring one second after release of air pressure (subject erect).

At 45° C., successive determinations in a given subject gave much more constant values than at 32° centigrade. There was still a wide variation in the values from subject to subject. The blood flow in the erect posture ranged between 24.0 and 77.0 c.c. per minute per 100 c.c. of foot. The increases resulting from assuming the erect posture ranged between two and three times the original supine level. The average increase was 2.5 times the original resting level obtained in the supine position. Again, only those observations made with the foot emptied in both the erect and recumbent positions are included.

In the four subjects, the blood flow was compared in the erect and supine postures at 38° centigrade. The blood flows in the erect posture ranged from 20 to 43 c.c. per minute per 100 c.c. of foot. As the foot was not emptied, no comparison can be made between the blood flow in the emptied foot in the erect and supine positions.

The question arose whether the rapid filling of the foot in the erect position resulted entirely from arterial inflow or from the combination of arterial inflow

and venous back flow from gravity. After the foot was emptied by air pressure, a cuff immediately proximal to the plethysmograph was inflated to 130 mm. of mercury. This was not sufficient to interfere with the arterial inflow, but it should have prevented venous back flow into the foot due to incompetent valves. The application of this cuff did not alter the rate of filling of the foot. It must be remembered that essentially normal subjects were being studied. Different results would be expected in subjects with incompetent venous valves.

The foot in the erect posture was largely emptied of venous blood by hydrostatic pressure 8 to 15 cm. greater than the venous pressure. At 32° C., the blood flow with hydrostatic pressure applied varied between 1.3 and 6.6 c.c. per minute per 100 c.c. of foot. The blood flow was not significantly different from that present with the patient in the horizontal position. Observations were made on four subjects at 45° centigrade. In three, there was no significant difference in the standing and lying positions. In the fourth, the blood flow in the erect position was reduced by the hydrostatic pressure to a level below that present with the patient supine (Table III).

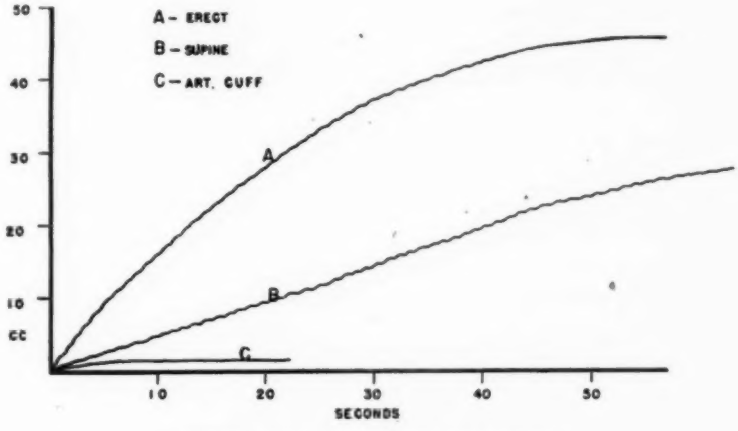

Fig. 4.—Blood flow tracings in arteriosclerosis. (Temperature of water 40° centigrade.) The dorsalis pedis, posterior tibial, and popliteal pulses were not palpable. The slow filling of the foot, even in the erect posture, is obvious. Note disappearance of arterial pulsations as foot fills.

Observations were made on three different days on one subject (L. C. in Tables II and III and Fig. 4) with moderately advanced arteriosclerosis obliterans, two weeks after a lumbar sympathectomy had been done. It seemed desirable to determine the effect of a postural increase in arterial pressure on the blood flow into a foot which was fed entirely by collateral circulation. The femoral pulse was present but the popliteal, posterior tibial, and dorsalis pedis pulses could not be felt.

He was studied at 40° C. rather than 45° C., to avoid possible tissue trauma. In a normal individual, rapid blood flow through the foot, when immersed in water at 45° C., acts as a cooling system to lower the temperature of the foot.

This cooling mechanism is greatly handicapped in the presence of obliterative vascular disease. His supine blood flow was 2.7 c.c. per minute per 100 c.c. of foot; on standing erect, the flow increased to 9.6, or about 3.5 times. The blood flow with the subject in the erect position, with pressure in the standpipe sufficient to empty the foot of its venous blood, was essentially identical with that obtained with the patient supine.

DISCUSSION

The relationship in man between the quantity of blood flowing through a part and the arterial pressure has never been thoroughly studied because of the lack of a convenient and physiologic method of increasing the arterial pressure. The observations recorded in this presentation are of interest in that they demonstrate that an increase in arterial pressure will cause an increase in blood flow through the skin, both in vessels which are partially constricted and in those which are completely dilated by heat. An increase in blood flow from a rise in arterial pressure was to be expected when the vessels were maximally dilated. The response to an increase in arterial pressure when the vessels are partially constricted could not have been predicted. On theoretical grounds it seemed possible that an increase in blood flow produced by a rise in arterial pressure might be compensated by vasoconstriction. The theory of local tissue control propounded by Lewis[6] would lead us to expect that the increased blood flow would wash out the "H substance" from the tissues, thus causing vasoconstriction and a return of the blood flow to the level present before the rise in arterial pressure. As far as we could determine, a sustained increase in blood flow was not followed by a tendency to vasoconstriction. At the end of a five-minute period in which the foot was emptied repeatedly, the blood flow into the empty foot remained at a high level. These observations were not entirely satisfactory and they should be repeated, using a mechanical device to empty the foot rhythmically.

The increase in flow at a temperature of 32° C., produced by raising the arterial pressure, does not occur because the vessels are mechanically paralyzed by the high arterial pressure. If the foot is placed in colder water, the blood flow decreases. If it is warmed, the flow increases. It would appear that the ability of the vessels of the foot to alter their caliber in response to changes in temperature is not altered.

In a system of rigid tubes filled with a simple solution of constant viscosity, the flow varies directly with the pressure driving the fluid. If the pressure is doubled the flow is doubled. Blood is not a simple solution, and the effective viscosity may change with the velocity of flow.[7] In our subjects the blood flow in the emptied foot was usually more than doubled when the mean pressure was doubled. Our methods of recording mean pressure and blood flow were too crude to allow us to be certain that this finding is significant. Green and collaborators,[7] in a study of the relationship between arterial pressure and blood flow in the perfused skin and muscle of dogs, stated that during a constant state of vasomotor activity increments of blood flow per increment of perfusion pressure in skin, and often in muscle, increased regularly from zero upward when flow

was measured immediately after establishment of the perfusion pressure. Wilkins and Eichna[8] demonstrated a rise in blood flow in the vessels of the forearm and calf dilated by a five-minute period of arterial occlusion. They found equal increments of pressure to cause equal increments in blood flow.

The demonstration that the blood flow increases as the arterial pressure rises is of interest in relation to the hemodynamics of hypertension. In a previous study,[5] it was pointed out that in hypertension the blood flow in the foot with the vessels maximally dilated is not increased above that found in normal subjects under similar conditions. This was interpreted to mean that, in response to a stimulus for maximal vasodilatation, the vessels of the foot in patients with hypertension were incapable of dilating as fully as those of normal persons. If the hypertension were lowered by an acute infectious disease, the vessels might then respond differently and dilate as well as those of a normal subject. The assumption that hypertension would cause an abnormally high blood flow in the foot when the vessels are dilated by heat, if they could react as normal vessels, is supported by the observations recorded in this paper.

The duration of the rapid blood flow produced by emptying the foot of blood while standing erect depends on the time that it takes to fill the foot. Once the foot is full, the increase in venous pressure balances the increase in arterial pressure. Maximum flow occurs when the vessels are fully dilated and the foot is empty. As it fills, peripheral resistance increases and the blood flow diminishes. When maximal dilatation was present, the period of time in which the blood flow was increased was short, rarely exceeding six to eight seconds. When vessels were not completely dilated, the duration of increased blood flow resulting from standing erect was longer and frequently exceeded fifteen to twenty seconds.

The increase in blood flowing to the empty foot when the patient is erect demonstrates the fundamental soundness of the exercises described by Buerger[10] for increasing the blood flow in the feet in persons with occlusive vascular disease. The foot is raised above the level of the heart to empty it of blood. It is then placed below heart level and the increased arterial pressure head created by gravity is unopposed for a time because the veins are empty. The flow in the foot is increased until the foot is filled. The disadvantages of these exercises lie in the fact that they can only be carried out for a relatively short time. The studies recorded in this paper suggest that a peripheral venous pump designed to empty the foot rhythmically while the patient was standing might be much more effective. The foot can be emptied in a few seconds without decreasing the flow appreciably below that normally present when the patient is lying down. During the next fifteen to forty-five seconds the foot would fill at a more rapid rate. Studies are now in progress to determine whether a peripheral venous pump has any clinical usefulness.

SUMMARY AND CONCLUSIONS

1. A method is described for measuring the arterial blood flow in the foot of the erect subject. This method primarily involves emptying the venous system of the foot by means of air pressure and recording the inflow of blood into the foot by means of a water plethysmograph.

2. Occlusion of the arterial inflow to the foot is followed by reactive hyperemia, but in order to obtain maximum dilatation with the water temperature between 32° and 38° C., the period of arterial occlusion must be much longer than is necessary to dilate the vessels in the forearm. Immersing the foot in water at 45° C. will cause complete vasodilatation.

3. The blood flow in the emptied foot with the subject erect must be compared with the blood flow in the emptied foot with the subject supine. When the patient is supine, the blood flow into the emptied foot is approximately 35 per cent faster than into the unemptied foot.

4. The mean arterial pressure in the foot is approximately doubled by motionless standing. This increase in arterial pressure when the subject is erect causes the blood flow into the emptied foot when the patient is in the upright position to be approximately twice that present under similar conditions when the subject is supine. The blood flow in the emptied foot increases when the patient is erect, both when the vessels are partly constricted by lowering the temperature and when they are completely dilated by heat.

5. The pressure required to empty the foot of its venous blood when the subject is erect does not reduce the blood flow greatly below that normally present when the subject is recumbent.

6. Observations were made on three different days in one patient with vascular disease in whom popliteal, posterior tibial, and dorsalis pedis pulses were absent. He had undergone a left paravertebral sympathectomy. The blood flow at 40° C. was about three and one-half times greater in the erect than in the supine posture.

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ELECTROCARDIOGRAM IN CHRONIC COR PULMONALE

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SINCE the publication by one of us (D. S. P.) of a paper on chronic cor pulmonale, we have become increasingly interested in the electrocardiographic features of this condition. We are now convinced that the electrogram is a real aid in the diagnosis of chronic cor pulmonale, and that frequently a diagnosis of this condition can be made by the electrocardiogram before it can be made by clinical methods.

In order to gain a better knowledge of the electrocardiogram in this condition, we have studied fifty cases of chronic cor pulmonale in which the diagnosis was confirmed by the clinical, x-ray, and electrocardiographic findings.

STANDARD LEADS AND UNIPOLAR EXTREMITY LEADS

P Wave.—In chronic cor pulmonale the P wave is usually higher than normal, particularly in Leads II and III (Table I, Figs. 1 and 2). In our series, the highest voltage was 3.7 mm. for P_2 and 3.0 mm. for P_3. The voltage and width of P_1 was not significantly altered. We believe that when the voltage of P_2 or P_3 is below 0.5 mm. the possibility of uncomplicated chronic cor pulmonale is practically excluded. Only one case in our series had such findings, and this case presented aortic atheroma as a complication.

When the net area of P_3 is greater than that of P_1, the mean manifest axis of P ($\hat{A}_P$) will be to the right of +60°. Fig. 7 shows that all but eight cases had an $\hat{A}_P$ of +60° or more, with an average of +69°. This figure would be increased to 71.6° had the case shown in Table I been excluded. In either event, the average is to the right of that found by Novelo[2] (+64°). In our series, the magnitude of $\hat{A}_P$ varies from 0.5 to 4.2 Ashman units, with an average of 2.36 units. We do not know the normal magnitude of $\hat{A}_P$.

The P in Lead V_F was positive in 97.9 per cent of the cases, diphasic in 2.08 per cent (only one case), and negative in no case (Fig. 3).

Our values for the voltage of P in Lead V_F are above the normal ones, if we calculate these values from the formula $V_F = \frac{\text{Lead II and Lead III}}{3}$. A histogram of the voltages of the P in Lead V_F is very similar to that of P_3. We think that a small or absent P in the V_F lead can exclude the possibility of chronic

Received for publication March 25, 1947.

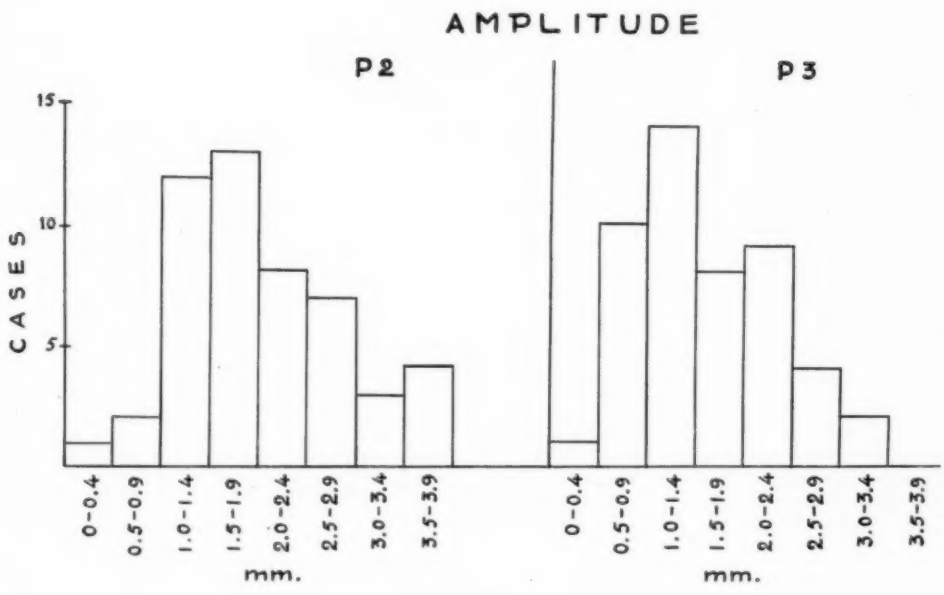


Fig. 1.

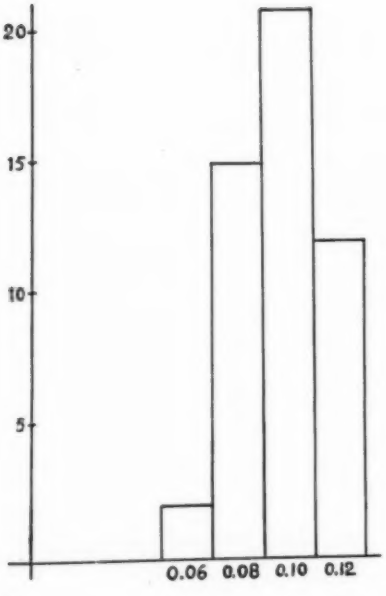


Fig. 2.

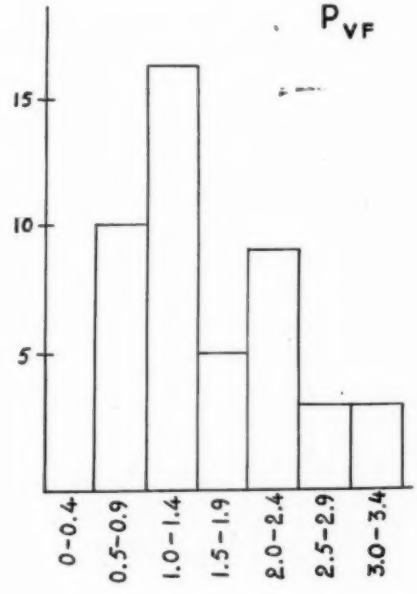


Fig. 3.

Figs. 1, 2, and 3.—Amplitude and width of the P wave in Leads II, III, and V_F. The P wave is higher than normal in 4 per cent of the cases in Lead II, in 30 per cent in Lead III, and in 40 per cent in Lead V_F. The width of P shows no significant changes.

cor pulmonale more readily than a high P in this lead can establish the diagnosis of such a condition, because some cases of congenital heart disease and rheumatic heart disease with tricuspid involvement can also present a high P in the V_F lead.

TABLE I. AMPLITUDE AND WIDTH OF THE P WAVES

	COR PULMONALE		NORMAL*
	AMPLITUDE (MM.)	WIDTH (SEC.)	AMPLITUDE (MM.)
P_1			
Max.	1.8	0.12	1.1
Med.	0.6	0.06	0.55
Min.	0	0	0
P_2			
Max.	3.7	0.12	2.5
Med.	1.9	0.09	1.25
Min.	0.8	0.04	0.3
P_3			
Max.	3.0	0.12	2.0
Med.	1.4	0.08	0.8
Min.	0.5	0.04	−1.0
P_{VF}			
Max.	2.13		1.5†
Med.	1.0		0.68
Min.	0.33		−0.23

One case complicated with aortic atheroma ($P_2 = 0$ and $P_3 = -0.5$ mm.).
*According to Ashman and Hull.[9]
†Calculated from formula $V_F = \frac{D_2 + D_3}{3}$.

In a previous paper,[1] the great frequency of a negative P in Lead V_L was mentioned. In the present series (Table II), the P wave of Lead V_L was negative in 54.4 per cent of the cases, diphasic with a preponderance of the negative phase in 13.1 per cent, isodiphasic in 8.7 per cent, isolectric in 6.5 per cent, and predominantly positive in 17.2 per cent. The P in this lead is frequently negative; but, when this sign is found alone, it is of secondary importance. On the other hand, we must emphasize the infrequence (17.2 per cent) of a positive P in the V_L lead in chronic cor pulmonale.

According to the shape of the P wave, we divided them into two main groups: "gothic" form (58 per cent) where the apex of the P wave was pointed, and the "romanesque" form (42 per cent) where the apex of the P wave was round.

Auricular T Wave.—The auricular repolarization wave (T_A) manifests itself as a slightly negative phase which follows the P wave. This wave is not easily detected because of its smallness or because it is superimposed on the QRS complex. In certain abnormal conditions, the P-R segment can show a negative displacement of 1 mm. or more. This could be related to disturbances of auricu-

lar repolarization, because of its similarity to the experimental tracings obtained when the auricular muscle is injured.

TABLE II. THE P WAVE IN LEAD V_L

DIRECTION	NUMBER OF CASES	PER CENT	
−	25	54.4	67.5
−/+	5	10.9	
+/−	1	2.2	
−	4	8.7	15.2
+	0	0	
±	6	6.5	
0			
−/++	1	2.2	17.2
+/(Flat)	7	15.0	

We use the terms "primary T_A" and "secondary T_A," after Wilson's terminology, in cases where the ventricular T wave changes. This author calls the changes "primary" when they are due to abnormal ventricular repolarization (myocardial damage) and "secondary" when they depend on a modification of the ventricular depolarization (ventricular hypertrophy and bundle branch block). We apply the term "secondary T_A" when a negative displacement of the P-R segment accompanies a P wave of high voltage (due to auricular hypertrophy); the term "primary T_A" is applied to a negative displacement of the P-R interval when it follows a notched P wave of normal or low voltage (due to auricular damage). In our series of cases (Fig. 4, and Table III), there was fre-

TABLE III. DISPLACEMENT OF THE P-R SEGMENT (AURICULAR T WAVE)

	NORMAL (MM.)	COR PULMONALE (MM.)
Min.	0	0
Med.	0.25	0.5
Max.	0.5	1.2

quently a negative displacement of the P-R segment in Leads II and III, which varied from 0 to 1.2 mm., with an average of 0.5 millimeter. These figures are above those given for normal individuals: 0.25 mm., average, and 0.5 mm., maximum. It is probable that most of our cases exhibited "secondary T_A"

and few of them "primary T_A," since the abnormal P-R segment is usually associated with high voltage P waves.

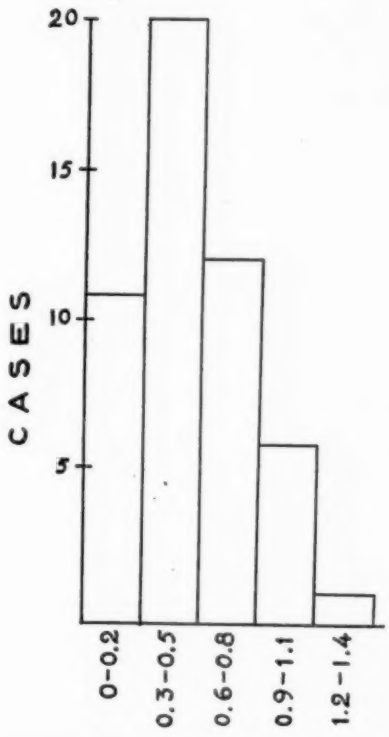


Fig. 4.—P-R segment. The negative displacement of the P-R segment exhibits a "secondary" auricular T wave, due to auricular hypertrophy.

P-R Interval.—The P-R interval was normal in every case. Therefore, the possibility of some complication (digitalis action, rheumatic heart disease, vagotonia, myocardial sclerosis, and so forth) must be investigated in patients with chronic cor pulmonale who show first degree A-V heart block.

Q and S Waves.—The high incidence of an S_1-Q_3 pattern and the rarity of a Q_1-S_3 pattern has been pointed out.[1] This was confirmed in our series: S_1 was present in 96 per cent, and Q_3, in 68 per cent of the cases (Fig. 5). One case showed a Q_1-Q_2-Q_3 pattern and eleven (22 per cent) cases showed an S_1-S_2-S_3 pattern. Meek and Wilson[3] have emphasized the presence of an S_1-Q_3 pattern in hearts with a clockwise rotation about their anatomic axis. In our cases such a rotation was more frequent (62 per cent) than among normal persons (29 per cent) (Table IV). If we diagnose a backward position of the apex of the heart in those cases having an S_1-S_2-S_3, as well as in those with S_1-S_2 pattern, who present marked clockwise rotation, the percentage of such a rotation (29 per cent) rises to 46 per cent, which is well above the figure among normal hearts.

R and S Waves.—The voltage of these waves is shown in Fig. 6. The average of the R wave (particularly R_1) was below normal (Table V). S_1 was greater and S_3 less than normal. The combination $R_1<R_2<R_3$ was present in 62 per cent of the cases, and that of $S_1>S_2>S_3$ was even more frequent (84 per cent). The association of both is considered abnormal by Holzmann[4] (pathologic dextro-type).

TABLE IV. ROTATION OF THE HEART ABOUT THE LONGITUDINAL AXIS

	NORMAL (PER CENT OF CASES)	COR PULMONALE (PER CENT OF CASES)
Clockwise	29	60
Counterclockwise	16	2
Without rotation	55	38

TABLE V. AVERAGE VALUES OF R AND S IN THE LIMB LEADS

	NORMAL* (MM.)	COR PULMONALE (MM.)
R_1	6.81	1.61
R_2	11.99	4.14
R_3	8.5	5.58
S_1	1.67	3.71
S_2	1.53	2.12
S_3	1.27	0.68

*According to Kossmann and Johnston.[10]

RS-T Segment and T Wave.—The RS-T segment (particularly in Leads II, III, and V_F) frequently (66.6 per cent) showed a negative displacement; it was sometimes isolectric (27.8 per cent), and rarely positive (5.53 per cent). One-half of the cases with negative displacement showed a "staircase" shape (the RS-T segment parallel to the isolectric line, but below it); the other half showed a downward slope of the RS-T segment, with a T wave which was either negative or diphasic. Negative (16 per cent), diphasic (− +) (48 per cent), and flat (18 per cent) T waves were mainly found in Leads III and V_F. The wave was positive in these leads only in a few cases (18 per cent) (Table VI). We emphasize that a diphasic T_3 of the − + type was more often seen than a negative T_3, which is usually considered one of the principal characteristics of chronic cor pulmonale. We do not know whether this diphasic T_3 was due to right ventricular hypertrophy, myocardial damage, or position of the heart. The presence of a negative T wave in Leads III and V_F in normal vertical hearts

with a forward position of the apex and clockwise rotation about their anatomic axis has been recently mentioned by Goldberger.[6]

Another QRS-T pattern was seen in Lead III with some frequency, but cannot be considered as pathognomonic of chronic cor pulmonale. It consisted of

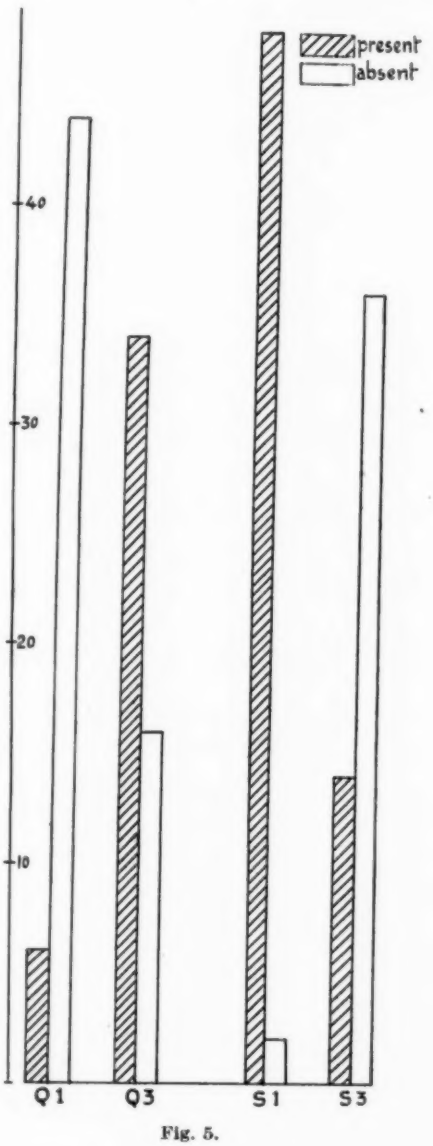


Fig. 5.

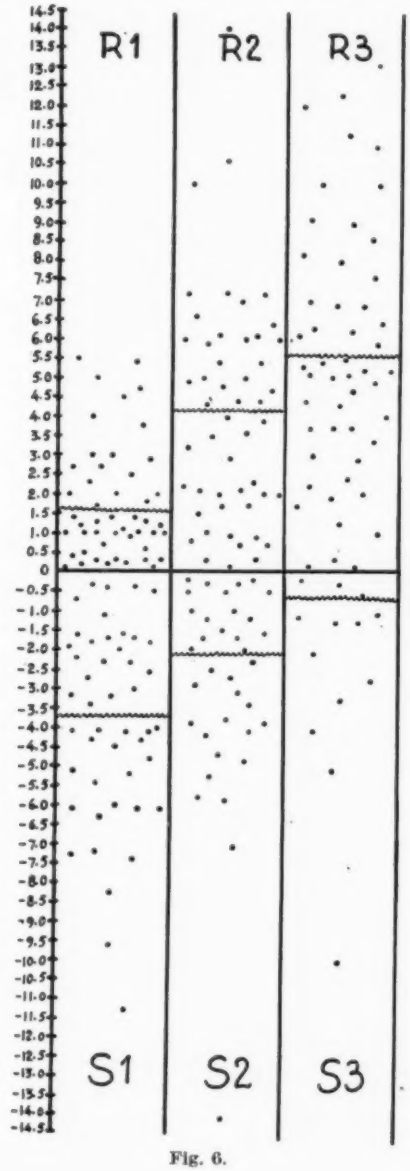


Fig. 6.

Fig. 5.—Q and S waves in the limb leads. Presence of S_1 in 96 per cent and of Q_3 in 68 per cent of the cases. Absence of Q_1 in 88 per cent and of S_3 in 72 per cent of the cases.

Fig. 6.—Amplitude of the R and S waves in the limb leads. Notice the small voltage of R_1 and S_3 in comparison with the high voltage of S_1 and R_3. For average values, see Table V.

(a) a small Q wave, (b) a high R wave ($R_3 > R_2 > R_1$), (c) a small or absent S wave, and (d) a "staircase" RS-T segment.

TABLE VI. DIRECTION OF RS-T SEGMENT AND T WAVE

	CASES	PER CENT
Lead I		
+	44	88
0	6	12
−	0	0
Lead III		
+	9	18
0	9	18
±	24	48 } 64
−	8	16 }

Mean Manifest Axis of QRS ($\hat{A}_{QRS}$).—In our cases, $\hat{A}_{QRS}$ lay on Bayley's Sextants 2, 3, 4, and 5, and every case except two fell between +90° and −90° (Fig. 7); the same distribution was found in a previous study of right ventricular hypertrophy.[5] We do not remember a case of pure chronic cor pulmonale (not complicated by *cor aortale*) which had its $\hat{A}_{QRS}$ on Sextants 1 or 6.

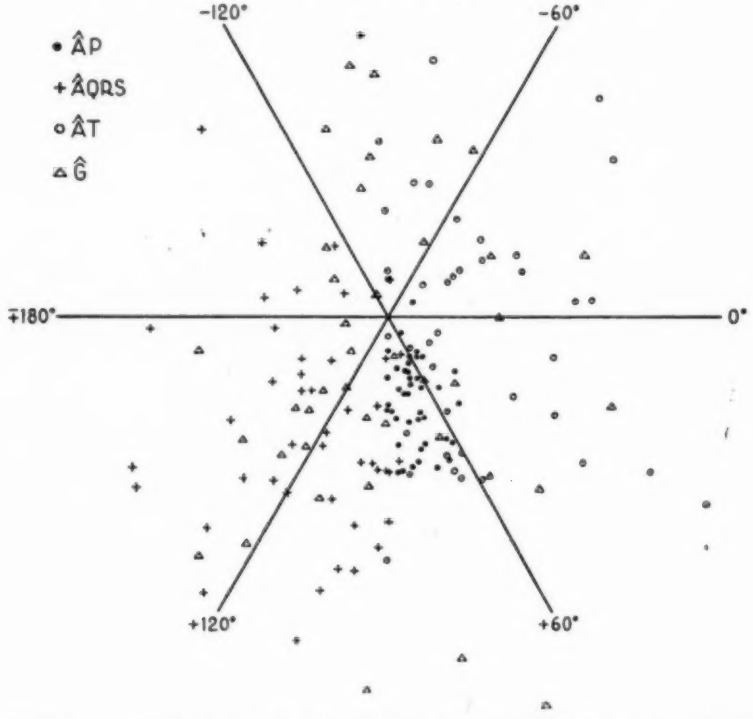


Fig. 7.—The mean manifest axis. $\hat{A}_P$ is to the right of + 60°, with an average of 71.6°. $\hat{A}_{QRS}$ falls between + 90 and − 90°, in Bayley's Sextants 2,3,4, and 5. $\hat{A}_T$ lies on Sextants 1,2,5, and 6 between + 90° and − 90°. *G* is distributed all over the system of Bayley with a certain predilection for Sextants 2,4, and 5.

Chronic cor pulmonale probably reduces the projection of the spatial vector $S\hat{A}_{QRS}$ upon the frontal plane, as compared with normal cases (Table VII). Forty per cent of our cases had a magnitude of $\hat{A}_{QRS}$ below the lower normal value, and none exceeded the upper normal.

TABLE VII. MAGNITUDE OF A_{QRS} AND G

	$\hat{A}_{QRS}$		G	
	NORMAL*	C.C.P.	NORMAL*	C.C.P.
Min.	3.5	1.0	2.5	0.6
Med.	6.3	4.46	13.0	4.53
Max.	12.0	9.0	23.0	12.5

*According to Ashman and Hull.[9]

Mean Manifest Axis of T ($\hat{A}_T$).—These lay on Sextants 1, 2, 5, and 6, between +90° and −90° (Fig. 7) (a fact which makes obvious their opposition to $\hat{A}_{QRS}$). This finding suggests "secondary" changes of T.

Ventricular Gradient (G).—The position of G varied greatly. It was distributed all over the system of Bayley, with a certain predilection for Sextants 2, 4, and 5 (Fig. 7). The mean magnitude of G was below normal values (Table VII). We do not know whether this was due to a peculiar position of the spatial vector SG or to an actual shortening of it.

The White-Bock Index: $(U_1 + D_3) - (D_1 + U_3)$.—This index gave normal figures in every case except three whose indices were below normal values (−16, −18, and −20 millimeters). Still, there was a preponderance of negative figures (Fig. 8).

Electrical Position of the Heart.—We divided our cases in two groups, according to Goldberger and Schwartz's classification[6]: vertical hearts (88 per cent), and horizontal hearts (2 per cent); in 10 per cent of the cases the electrical position could not be determined.

We shall only describe the vertical group, which was divided into three subgroups: (a) *apex forward* (twenty-nine cases); (b) *apex backward* (six cases); and (c) *apex intermediate* (nine cases).

Subgroup *a* showed a minimal dispersion of $\hat{A}_{QRS}$ and a maximal dispersion of $\hat{A}_T$. Subgroup *b* showed a maximal dispersion of $\hat{A}_{QRS}$ and a minimal dispersion of $\hat{A}_T$. Subgroup *c*, with an intermediate anatomic position, showed intermediate grades of dispersion of $\hat{A}_{QRS}$ and $\hat{A}_T$ (Fig.9). These characteristics were probably due to a spatial relation among $S\hat{A}_{QRS}$, $S\hat{A}_T$, and SH, as well as to the spatial relations between the frontal plane and the first two vectors (see Discussion).

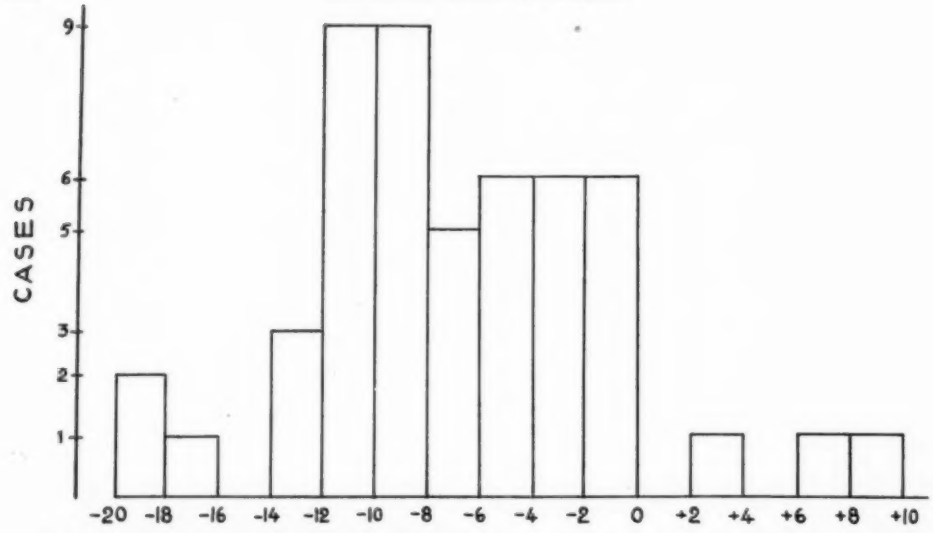
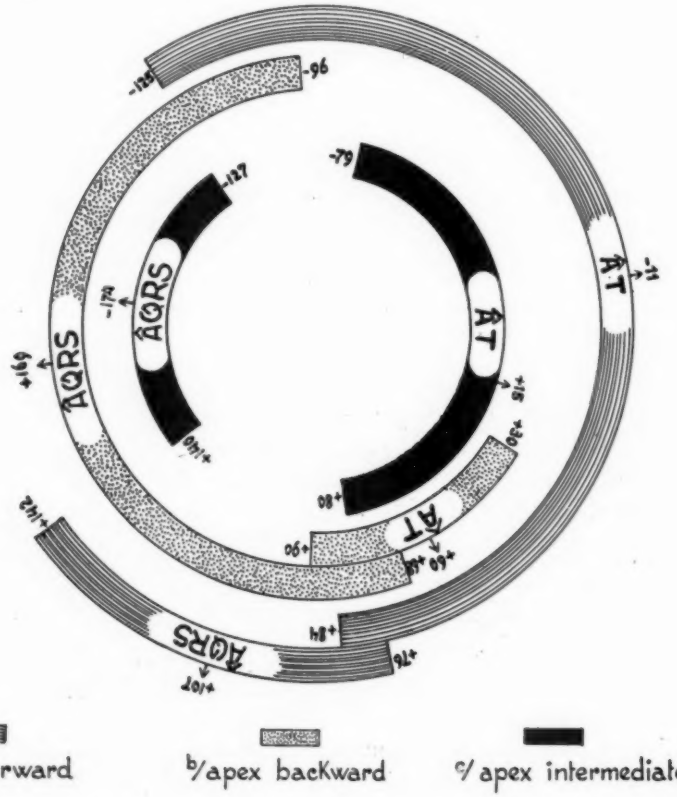


Fig. 8.—The White-Bock index. The index $(U_1 + D_3) - (D_1 + U_3)$ gives a preponderance of negative values, ranging from + 8.5 to − 19.0 (average of − 4.63). Eighty-two per cent of the cases lie between 0 and − 12.



a/apex forward b/apex backward c/apex intermediate

Fig. 9.—Relation between $\hat{A}_{QRS}$ and $\hat{A}_T$ in vertical hearts. *a*, Apex forward: minimal dispersion of $\hat{A}_{QRS}$ and maximal dispersion of $\hat{A}_T$. *b*, Apex backward: maximal dispersion of $\hat{A}_{QRS}$ and minimal of $\hat{A}_T$. *c*, Apex intermediate, intermediate grades of dispersion of $\hat{A}_{QRS}$ and $\hat{A}_T$.

Subgroup *a* presented an endocardial pattern which appeared frequently in Lead V_R and always in Lead V_L; this is in accordance with Goldberger's findings.[6] Against Goldberger's expectations, only one case in subgroup *b* showed posterior epicardial pattern of the QR type in Leads V_R and V_L. A great number of cases in subgroup *c* showed a ventricular complex of the qR type in Lead V_R. This qR complex must probably be considered the result of a semidirect lead from the right auricle in cases of right ventricular hypertrophy, and not Goldberger's left ventricular epicardial pattern.

PRECORDIAL LEADS

P Wave.—A diphasic P wave was usually seen in Leads V_1 through V_3, but was rare in Leads V_4 through V_6 (Table VIII). According to the form of this diphasic wave we speak of P waves of the + −, ++ −, or + −− type, mentioned in order of their frequency. There were some negative P waves in the right precordial leads, but they were never found beyond the V_3 position. The negative P waves described by some authors[7] as being present all over the precordium are probably due to the use of the left leg as an "indifferent" electrode (high P in Lead V_F). As a whole, the changes of the precordial P waves are less significant than those of the standard and unipolar extremity leads.

R and S Waves.—The average voltage of R in Leads V_2 through V_6 was low, and that of S was high in Leads V_3 through V_6 (Table IX and Fig. 10). The average voltage of R + S was normal in cases of chronic cor pulmonale; this suggests a change in the position of the heart rather than an extracardiac factor (pulmonary emphysema) as a cause for the low voltage of R.

TABLE VIII. PRECORDIAL P WAVES

	+	++ / −	+ / −	FLAT	+ / − −	−	BIFID FLAT	FLAT AND NOTCHED
V_1	8	7	16	0	6	8	3	0
V_2	11	6	17	0	3	7	5	0
V_3	21	0	7	7	1	1	8	3
V_4	20	0	1	13	1	0	7	8
V_5	17	0	0	18	1	0	1	11
V_6	15	0	0	22	1	0	0	11

T Wave.—A negative T wave was found in 59 per cent of cases in Lead V_1, and in 46 per cent in Leads V_1 and V_2. The T wave was usually positive in Leads V_3 through V_6 (Table X). A negative T wave in a precordial lead was always accompanied by negative T waves in the preceding precordial leads. The intrinsic deflection of Leads V_1 and V_2 was delayed in only 30 per cent of cases with a negative T wave in such leads.

TABLE IX. R AND S WAVES IN THE PRECORDIAL LEADS

		R		S	
		NORMAL* (MM.)	C.C.P. (MM.)	NORMAL* (MM.)	C.C.P. (MM.)
V_1	Max.	9.6	21.6	24.0	30.0
	Med.	4.16	3.9	11.05	9.3
	Min.	1.0	0.0	3.4	0.0
V_2	Max.	20.8	18.6	38.8	51.0
	Med.	9.05	4.5	16.23	15.9
	Min.	4.0	0.0	3.0	0.0
V_3	Max.	54.6	40.5	22.0	48.6
	Med.	16.7	5.4	9.05	22.8
	Min.	6.0	0.0	0.0	0.0
V_4	Max.	46.0	42.0	16.0	49.5
	Med.	22.31	8.4	5.32	19.8
	Min.	12.2	0.0	0.0	0.0
V_5	Max.	33.0	39.9	9.6	34.5
	Med.	18.78	9.9	1.93	12.3
	Min.	8.8	0.0	0.0	0.0
V_6	Max.		36.0		22.5
	Med.		7.8		7.5
	Min.		0.3		0.0

*Kossmann and Johnston.[10]

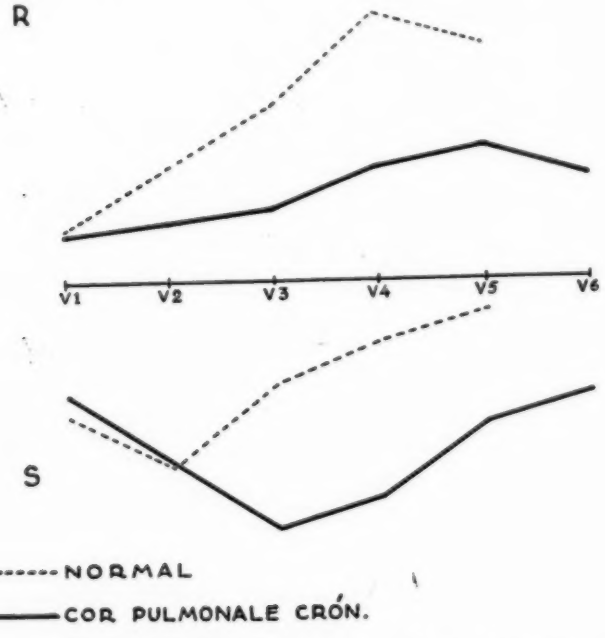


Fig. 10.—Precordial R and S waves. Low voltage of R and high voltage of S. The average voltage of R + S is essentially normal.

The Intrinsic Deflection of Right Precordial Leads.—Its delay was less frequent (fourteen cases) than we should expect, a priori. Five of these fourteen cases had a complication that by itself could explain the delay of the intrinsic deflection. These complications were mitral stenosis, tricuspid insufficiency, mitral calcification, aortic aneurysm with compression of the pulmonary artery, and aneurysmal dilatation of the pulmonary artery. These delayed deflections were present very frequently in ventricular complexes of the qR type (76.9 per cent), even though a qR complex was rather rare in Leads V_1 and V_2.

TABLE X. PRECORDIAL T WAVES

	+	−	∓	FLAT
V_1	9	29 (59 per cent)	3	8
V_2	16 (32 per cent)	23 (46 per cent)	4	7
V_3	24 (49 per cent)	13 (26.5 per cent)	1	11
V_4	28 (56 per cent)	8	1	13
V_5	26 (53 per cent)	4	1 (±)	18
V_6	31 (62 per cent)	1	0	18

Cor Pulmonale With Cor Aortale.—Rarely is there a small (less than 1.0 mm.) or absent S wave in Leads V_5 or V_6. Such a condition was found in twelve cases (24 per cent) and nine of them (75 per cent) showed the following complications of the "cor aortale" type: aortic sclerosis; cardiac sclerosis; coronary heart disease; chronic myocarditis; arteriosclerosis; essential hypertension; aortic atheroma; aortic sclerosis; and arterial hypertension. On the other hand, only 15.7 per cent of cases with an S wave of more than 1.0 mm. in Leads V_5 or V_6 were complicated by " cor aortale."

DISCUSSION

Chronic cor pulmonale may give a large number of electrocardiographic changes in the limb as well as in the precordial leads. These changes are difficult to evaluate, so we shall discuss them separately first, and then consider the changes seen in chronic cor pulmonale as a whole.

The right deviation and increase of $\hat{A}_P$ could readily be ascribed to right auricular hypertrophy, but the direction of $\hat{A}_P$ is evidently influenced by the position of the heart, and P can augment its voltage in a reversible, transitory way. We have already mentioned the difficulty in considering a prominent T_A as "primary" or "secondary" in origin.

The changes of the precordial P waves are not necessarily due to auricular abnormalities. The descent of the diaphragm in an emphysematous patient lowers the heart and leaves the precordial positions C_1 and C_2 in a relatively higher position, thus producing a negativity in the final portion of the P wave.

A right deviation of $\hat{A}_{QRS}$ is too readily ascribed to right ventricular hypertrophy. We believe it is the result of clockwise rotation of the heart about SH, whether this is produced by right ventricular dilatation (which so often accompanies right ventricular hypertrophy) or is merely the result of a vertical position of the heart.

The smallness of $\hat{A}_{QRS}$ and G could be related to ventricular myocardial damage, but we must not forget the influence of the conducting medium (emphysematous lungs) and the even more important influence of a backward displacement of the heart's apex, which makes $S\hat{A}_{QRS}$ lie perpendicular to the frontal plane. The smallness of R in the precordial leads is accompanied by normal R + S voltages, thus making it unsafe to use the term "low voltage" for the precordial leads.

We must be cautious in our interpretation, even when we find a delayed intrinsic deflection. The difficulty in detecting the intrinsic deflection in the right precordial leads has been mentioned in a previous paper.[8] The normally delayed activation of the pulmonary conus could give a delayed intrinsic deflection in Leads V_1 or V_2 in certain cases in which the heart is ptosed or the pulmonary conus dilated. Under such circumstances, a delayed intrinsic deflection could not be considered to be the direct result of right ventricular hypertrophy. We wish to emphasize that a delayed intrinsic deflection in chronic cor pulmonale may frequently be due to a complication affecting the right ventricle, as well as to the pulmonary condition.

A negative T_3 could be due to myocardial damage, but we have to remember its presence in normal hearts, and the fact that this wave can be made negative by nothing more than lowering of the diaphragm (deep inspiratory movement). Right ventricular hypertrophy may produce a negative displacement of RS-T_2 and RS-T_3, but such displacement, when slight, might be normal and possibly related to a vertical position of the heart.

We believe that a negative T wave in the right precordial leads is largely due to the position of the heart and not entirely to right ventricular hypertrophy, because of the low incidence of a delayed intrinsic deflection accompanying such negative T waves.

It is probable that the changes of R and S in the precordial leads are due to a clockwise rotation of the heart about SH, because (1) of the higher incidence of this type of rotation in chronic cor pulmonale (62 per cent against 29 per cent in normal hearts), and (2) of the frequent finding of transitional complexes which are shifted to the left and are found in Leads V_5 or V_6 instead of in Lead V_3 as is normal.

In relation to the form of dispersion of $\hat{A}_{QRS}$ and $\hat{A}_T$, let us remember that a backward situation of the apex makes $S\hat{A}_{QRS}$ lie roughly perpendicular to the frontal plane, so a greater dispersion of $\hat{A}_{QRS}$ is to be expected. The inverse relation between the dispersion of $\hat{A}_{QRS}$ and that of $\hat{A}_T$ suggests that, at least in chronic cor pulmonale, the corresponding spatial vectors are perpendicular to each other.

It follows from these considerations that the position of the heart greatly influences the shape of the electrocardiogram in chronic cor pulmonale. The position which the heart assumes is determined originally by the pulmonary emphysema, and later, by the strain which the right cavities undergo.

Pulmonary emphysema has several definite effects upon the heart: It causes the heart (1) to assume a vertical position, and (2) to descend as a result of the lowering of the diaphragm; (3) it produces clockwise rotation of the heart about SH, and (4) backward displacement of the apex; (5) it also produces disturbance in the transmission of the electrical potential of the heart.

1. The vertical position of the heart produces a slight deviation of $\hat{A}_{QRS}$ and $\hat{A}_P$ to the right, with subsequent increase of the P wave in Leads II, III, and V_F, and causes the P wave of Lead V_L to become negative.

2. The descent of the heart contributes to the appearance in the first two precordial leads of a negative T wave, a diphasic or negative P, and possibly a late R_2 due to activation of the pulmonary conus.

3. The clockwise rotation of the heart about SH produces a considerable deviation of $\hat{A}_{QRS}$ to the right with the appearance of an S_1-Q_3 pattern, negative values of the White-Bock index, disappearance of S_3, transitional shape of the ventricular complexes in V_5 and V_6 (with lowering of R and deepening of S), and negativity of T_3 and the RS-T segments in Leads II, III, and V_F.

4. The backward displacement of the heart's apex gives diphasic complexes in the limb leads, and small $\hat{A}_{QRS}$ and G, and exaggerates any deviation of $\hat{A}_{QRS}$ which may exist.

5. The disturbance in the transmission of the heart's potential, due to the pulmonary condition, might explain the smallness of $\hat{A}_{QRS}$ and G.

Strain on the right cavities exaggerates almost every change produced by the position of the heart, and produces new modifications of its own. Hypertrophy of the right cavities accentuates the right deviation of $\hat{A}_P$ and $\hat{A}_{QRS}$, the voltage of P in Leads II, III, and V_F, as well as that of S_1 and Q_3, the negativity of P in Leads V_L and in the precordial leads, the negative value of the White-Bock index, the smallness of R in V_5 and V_6, the depth of S in these leads, the negativity of T in Leads III, V_1 and V_2, and finally that of S-T in Leads II, III, and V_F. Strain of the right cavities by itself produces notching and slurring of P, possible widening of P, and delay of the intrinsic deflection.

If the electrocardiogram shows only the signs of a change in position of the heart, it is unsafe to speak of cor pulmonale; even though the pulmonary emphysema has affected the heart to the extent that it has changed its position, it may not yet have produced heart disease. If the electrocardiogram shows the signs of strain upon the right cavities (whether these are functionally sufficient or insufficient), we can speak of cor pulmonale because there is then a relationship between pneumopathy and cardiopathy.

Unfortunately, almost every change of the electrocardiogram of chronic cor pulmonale with only differences of grade can be produced by alteration of the position of the heart, as well as by the strain upon the right cavities. The final interpretation of the electrocardiographic findings rests upon the experience of the interpreter of the electrocardiogram.

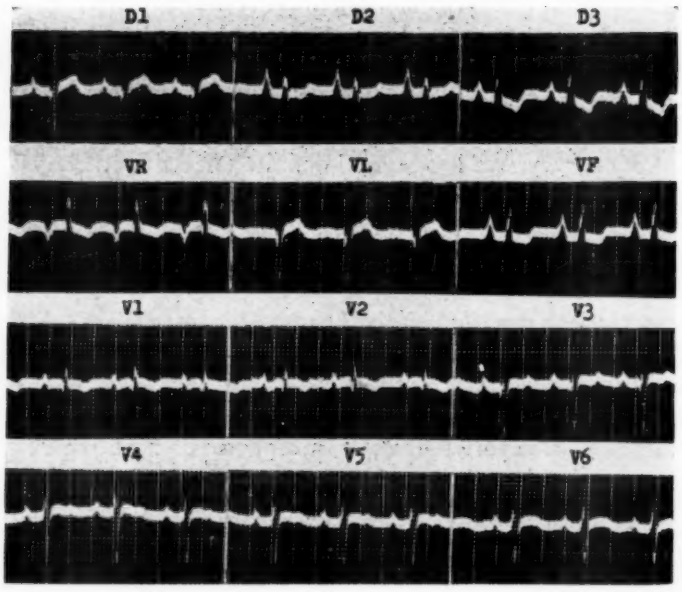


Fig. 11.—This is a typical tracing of chronic cor pulmonale. Notice the signs of right auricular hypertrophy ($\hat{A}_P = +65°$; $P_2 = 3.7$ mm.; gothic P wave in Leads II, III, and V_F; diphasic P wave in V_1 and V_2; prominent auricular T wave in Leads II and V_F) and those of right ventricular hypertrophy ($\hat{A}_{QRS} = +140°$; qR complex in V_R and V_L; delayed intrinsic deflection in V_L, deep S wave in V_5 and V_6; small R wave from V_3 to V_6; negative T wave in Lead III, V_1 and V_2; diphasic ST-T in Leads II and V_F).

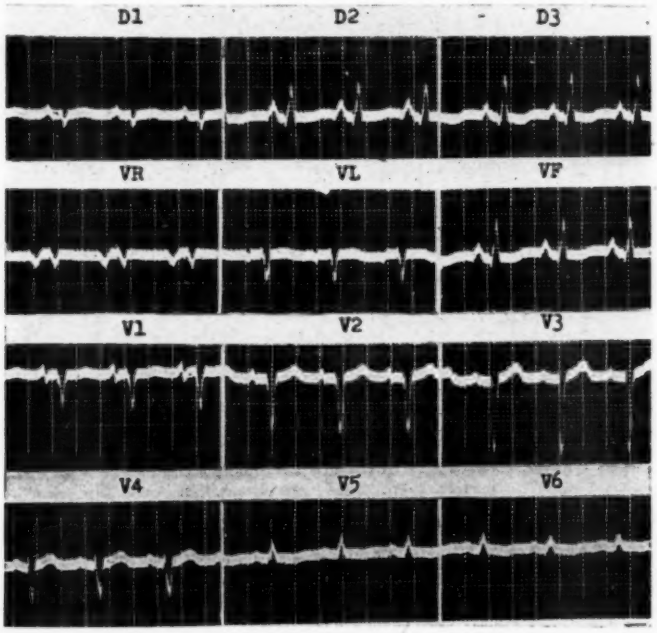


Fig. 12.—Tracing of a case of chronic cor pulmonale with cor aortale (arterial hypertension in this case). The first is diagnosed because of the P pulmonale (Leads II, III, and V_F), prominent auricular T, small precordial R waves, and diphasic ST-T (Leads II, III, and V_F). The second is strongly suggested by the absence of S in V_5 and V_6 (75 per cent of our cases without S in V_5 or V_6 were complicated by cor aortale).

SUMMARY

After the study of the electrocardiograms of fifty cases of chronic cor pulmonale, we consider that the principal diagnostic signs (see Fig. 11) are: (1) high and peaked P waves with prominent auricular T waves in Leads II, III, and V_F; (2) negative P waves in V_L; (3) right deviation and a decreased value of $\hat{A}_{QRS}$; (4) a small ventricular gradient (frequently deviated); (5) signs of clockwise rotation of the heart (S_1-Q_3) and backward position of its apex (S_1,S_2, and S_3; S_1 and S_2 with right deviation of $\hat{A}_{QRS}$); (6) diphasic (of the $- +$ type) or negative T waves in Leads III, II, and V_F; (7) small R waves in the precordial leads; (8) deep S waves in the left precordial leads; (9) diphasic (of the $+ -$ type) or negative P waves in the right precordial leads; and (10) negative T waves in the right precordial leads.

In the differential diagnosis, we emphasize that:

(1) The delay of the intrinsic deflection in the right precordial leads is frequently attended (36 per cent) by a complication which gives rise to further strain on the right ventricle.

(2) The absence or diminished amplitude of the S wave in the left precordial leads is frequently attended (75 per cent) by a complication of the "*cor aortale*" type (Fig. 12).

(3) A QS complex, usually in the right precordial leads, a W-shaped complex, or a deep Q wave in these leads is a frequent finding (36 per cent) in chronic cor pulmonale, without clinical signs suggestive of a myocardial infarct or a dead zone.

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THE FAMILIAL INCIDENCE OF RHEUMATIC FEVER

I. A Discussion of the Relationship Between a Positive Family History and the Development of Rheumatic Fever in Individuals of Military Age

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IN THE etiology of rheumatic fever, two fundamental mechanisms have been thought to play a role: contagion and heredity. It can hardly be doubted, in the face of actual epidemics of rheumatic fever associated with hemolytic streptococcus infection, that contagion plays a part both as an inciting factor in the development of the "initial" attack of rheumatic fever and in the exacerbation of the disease process in recurrent rheumatic fever. The fairly factual data on the infectious origin of rheumatic fever are not paralleled by similar material to support the role of heredity, although Wilson[1] has attempted to place the role of heredity on a firm statistical basis. She has stated: "It would seem fair to conclude from the genetic analysis of our data that the susceptibility for rheumatic fever is transmitted as a single autosomal recessive gene."[1, p. 53] In further consideration of the hereditary mechanism, attention must necessarily be placed on the unusual age distribution of the disease, particularly its sparing of children in the early years of life. As Paul[2, p. 96] has stated, "the infant must grow up to become rheumatic." Thus, if we are to accept the hereditary mechanism as dominant, might we not believe that it is a "susceptibility" of some obscure type that is inherited, according to Wilson's genetic hypothesis, and that the "growing up" phase represents the development of some sensitizing mechanism, that is, the development of hypersensitivity? Certain it is that most phenomena of the rheumatic state appear to have a basic allergic mechanism (Rich and Gregory[3] and Akiawa[4]). Therefore, both Wilson and Paul have emphasized the need for further studies on the familial aspects of rheumatic fever.

RÉSUMÉ OF PUBLISHED DATA

The problem of familial incidence in rheumatic fever, simply stated, is the problem of separating hereditary from contact factors. Each separately, or both operating simultaneously, may play a role either in favoring the initial attack

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Received for publication March 11, 1947.

or in precipitating recurrent attacks. The role of heredity in rheumatic fever has been supported by the following studies and observations.

1. The similarity in susceptibility to rheumatic fever of identical and fraternal twins, (Wilson,[1] Irvine-Jones,[5] and Kaufmann and Scheerer[6]). These analyses have been fairly uniform in showing that identical twins behave similarly genetically; that is, either both do contract rheumatic fever, or both do not. However, this is not always the case, as Paul[2, p. 90] has pointed out.

2. Genetic analysis of rheumatic families in relation to Mendelian prediction rates in various types of gene transmission (Wilson and Schweitzer[7]).

Studies such as these form the basis for Wilson's thesis of "autosomal recessive gene transmission" to which we have referred. From a critical analysis of these studies, Paul has concluded that "some inherited relationship exists between parental rheumatic fever and that of the siblings."[2, p. 90] More indirect evidence of the operation of heredity is obtained from Paul's consideration of the age at which second members of a rheumatic family acquire their initial attack. This occurs most often at an older age than that of the first member and is difficult, actually, almost impossible, to explain on the basis of contagion alone. It may be more logically explained on the basis of a gradually developing susceptibility of post-streptococcal origin.

The justification for the presentation of our data lies in the opportunity to inquire into the history of a large number of young adult rheumatic fever patients who have been separated for a varying period of time from the family contact. The history of the individual *following the break from family contact* affords an important method of separating hereditary influences from the factors of contagion.

SOURCE OF MATERIAL

It is the purpose of this communication to present observations on the occurrence of rheumatic fever, both initial and recurrent attacks, in relation to familial and postfamilial contacts. In contrast to the observations of Wilson and of Paul, who studied children in a relatively small number of families, this study is concerned with young adults of military age from a large number of families distributed widely over the United States. As controls, a group of tuberculous patients, a group of healthy physicians, and a group of patients in a veterans' hospital were studied.

Four separate series of patients form the basis for the present study. In each group, personal interviews were conducted by one of us, and information relative to previous rheumatic fever and family history tabulated. The composition of the four groups was as follows:

Group 1: 3,594 patients with rheumatic fever, who were interviewed over a period of twenty months in 1944 and 1945, in a naval hospital devoted almost entirely to the treatment of this disease.

Control Group 2: 519 patients of military age with tuberculosis who were seen in the same naval hospital.

Control Group 3: 254 healthy physicians who were working in a large general civilian hospital.

Control Group 4: 624 patients on the general, medical, and surgical wards of a veterans' hospital.

Groups 1 and 2 consisted of enlisted and officer personnel sent to the naval hospital for treatment. They were representative individuals from installations and ships of the United States Navy throughout the world.

RESULTS OF STUDY

The results of our observations are summarized in Tables I and II.

TABLE I. COMPARISON OF FAMILIAL INCIDENCE IN THE RHEUMATIC FEVER GROUP WITH CONTROL GROUPS

	NUMBER	PER CENT
Group 1 Rheumatic Fever Patients Total 3,594		
(a) Total patients with "initial" attack during military service (and therefore after separation from family)	2,819	78.4
(b) Total patients with "recurrent" attack during military service (initial attack occurred at home)	775	21.6
(c) Total patients with "initial" attack in service; family history positive	238	6.3 of total
(d) Total patients with "recurrent" attack in service; family history positive	354	9.8 of total
(e) Total patients with "initial" and "recurrent" attacks in service, family history positive; (*c*) plus (*d*)	592	16.4 of total
(f) Percentage of patients with "initial" attacks (2,819) with family history positive (238); (*c*) divided by (*a*)		8.4
(g) Percentage of patients with "recurrent" attacks (775); with family history positive (354); (*d*) divided by (*b*)		45.6
Control Group 2 Tuberculous Patients Total 519		
(a) Total patients with history of previous rheumatic fever	21	4.0
(b) Total patients with rheumatic fever before break from family	9	1.7
(c) Total patients with positive history of rheumatic fever in family	9	1.7
Control Group 3 Healthy Physicians Total 254		
(a) Total physicians with history of previous rheumatic fever	15	5.9
(b) Total physicians who had rheumatic fever before break from family	8	3.5
(c) Total physicians with positive history of rheumatic fever in family	8	3.5
Control Group 4 General Patients in a Veterans Hospital Total 624		
(a) Total general patients who had had Rh. F.	40	6.4
(b) Total general patients who had Rh. F. before break from family	23	3.7
(c) Total general patients with positive history of Rh. F. in family	15	2.4

TABLE II. THE FAMILIAL INCIDENCE OF RHEUMATIC FEVER IN THE FOUR GROUPS WHEN FAMILIAL CONTACT IS CONSIDERED ALONE

	NUMBER	PER CENT
Group 1		
Incidence of family history in patients with "initial" attacks of rheumatic fever; that is, while still in contact with the family		45.6
Total rheumatic fever patients ("initial" attack at home)	775	
Total family history positive	354	
Control Group 2		
Incidence of familial history in tuberculous patients who had had rheumatic fever while still in contact with family		42.9
Total tuberculous patients with rheumatic fever	21	
Total with family history positive	9	
Control Group 3		
Incidence of familial history in physicians who had had rheumatic fever while still in contact with family		53.3
Total physicians with rheumatic fever	15	
Total with family history positive	8	
Control Group 4		
Incidence of familial history in general patients in a veterans hospital who had had rheumatic fever while still in contact with family		37.0
Total veterans' hospital patients with rheumatic fever	40	
Total with family history positive	15	
Average familial incidence for all groups		44.7

Comment: (1) In Group 1, Table I, 16.4 per cent of all patients with rheumatic fever had a positive family background; 45.6 per cent of rheumatic fever patients with "recurrent" attacks had a positive family background. In the three control groups, patients with tuberculosis, healthy physicians, and patients in a general veterans hospital, the incidence of a positive family history of rheumatic fever was 1.7 per cent, 3.5 per cent, and 2.4 per cent, respectively. These figures are not, to our knowledge, unlike those in previously published reports, and call attention again to the definite importance of the family in the etiology of rheumatic fever.

(2) Of the rheumatic fever patients who developed an "initial" attack after separation from the family, 8.4 per cent had a positive family background, while 91.6 per cent of these patients had no knowledge of any occurrence of the disease within the family. It would appear that the actual attack rate, as exemplified in this large group of military personnel separated from familial contact, was determined by external factors, such as environment and infection, rather than by hereditary or familial factors.

(3) Table II illustrates the familial incidence in those patients who had had rheumatic fever while still in contact with family. In these groups, the incidence of a positive family history (44.7 per cent, average) is considerably higher than the incidence (16.4 per cent, average) in the rheumatic patients of Group 1. This high incidence shows the importance of a factor or factors which increase the tendency to develop rheumatic fever while in the home. It should be noted

that these similarly high percentages were obtained by random sampling of widely separated and dissimilar control groups. It is of great importance to note that none of the patients in Control Groups 2 and 3 who had rheumatic fever at home developed later attacks. It may be assumed that the high percentage of familial incidence in those patients who developed the rheumatic state while in contact with the family was due to contact in the home, in the same way that the high percentage of patients who developed rheumatic fever without a family history was due to contact with an inciting agent in the crowded quarters of the barracks.

It is certainly not within the scope of this paper to enlarge upon the nature or modus operandi of the infectious agent or to elaborate upon the possibility of a sensitization mechanism. We believe, however, that attention should be called to the disparity between the low familial incidence in "initial" attacks (Table I, Group 1) occurring after separation from the family (6.3 per cent) and the high familial incidence in those groups (Table II) who developed the "initial" attack while in contact with the family (44.7 per cent, average for the four groups).

In the military service the vast majority of cases of rheumatic fever developed in the training camps, where crowding in barracks permitted epidemics of hemolytic streptococcus infection to occur. Undoubtedly such epidemics occurred from contact. Is it possible that those patients who developed rheumatic fever prior to military service might have done so from contact with the streptococcus in the home? One may, therefore, raise the question whether the family carries a significantly larger place in the etiology of rheumatic fever than a source of contact. Is the family different from the barracks or a training center as a locus for contact with the inciting infectious agent? The further study of the 78.4 per cent of patients in Group 1 who developed rheumatic fever after separation from the family will help to answer the problem of hereditary susceptibility versus poststreptococcal sensitivity as the cause of recurrent attacks.

CONCLUSION

1. Four groups of young adults have been interviewed. One group of rheumatic fever patients (3,594) and three groups of nonrheumatic individuals (1,397), serving as controls, formed the basis of the study.

2. Group 1 shows that approximately 78 per cent of the patients with "initial" rheumatic fever developed the disease after separation from the family. We raise the question whether this indicates some agent outside of the family as the chief factor operative in the etiology of rheumatic fever.

3. The tuberculous patients and healthy physicians who had "initial" attacks of rheumatic fever while at home did not develop secondary attacks after separation from the family.

4. It is noted in Groups 2, 3, and 4, the controls, that the individuals who developed rheumatic fever prior to separation from the family showed a similar family incidence, and that this incidence does not differ greatly from that found in the rheumatic patients studied.

5. The high familial incidence of rheumatic fever, averaging 44.7 per cent in those who developed the disease while still at home, seems to indicate that

there is some factor within the family. Is this factor a hereditary susceptibility or contact with the inciting agent in the home?

6. The great need for further data on the subject of heredity versus environment is evident.

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THE FAMILIAL INCIDENCE OF RHEUMATIC FEVER

II. A Statistical Study of the Familial and Personal History of Rheumatic Fever

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A POSITIVE familial history of rheumatic fever could be of importance in determining the risk of an individual developing the disease in several conceivable ways: first, because it might indicate a fundamental and inherited familial susceptibility; second, because it might indicate some social, economic, or climatic environment which predisposes to rheumatic fever and is shared by the family; or, third, it could influence the risk because a prerequisite to rheumatic fever might be an infection which is transmitted by contact. *It would seem justifiable to assume that any fundamental and inherited susceptibility which increases the risk of developing the disease by an individual should do so not only while the individual remains at home, but also after he has left the family environment.* In order to learn whether ot not this is true, we have made a study of the familial history in patients who did or did not develop rheumatic fever while still in contact with the family or after they had left their homes. The study also included an inquiry into the question of whether or not a positive personal history of the disease while still at home tended to predispose the individual to a later attack after leaving home.

METHOD OF ANALYSIS

The material studied in Part II is identical with that considered in Part I of this paper, but the material is handled on a contingency basis rather than by the comparative and descriptive method which was used in Part I. The *chi-square* test of significance was used throughout Part II.

Two populations were sampled: (A) individuals who developed rheumatic fever in the Army or Navy, most of whom were under treatment at the Corona Naval Hospital when investigated; and (B) individuals who did not develop rheumatic fever after separation from the family, these being (1) individuals under treatment for tuberculosis at the Corona Naval Hospital, (2) intern and

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Received for publication March 11, 1947.

resident physicians of a large civilian hospital, and (3) Army personnel on the medical and surgical wards of the Birmingham General Hospital. The total number of individuals studied was 4,991. Table I shows the number of individuals in each of the foregoing groups:

TABLE I. NUMBER OF PATIENTS STUDIED IN THE VARIOUS GROUPS

		TOTAL
Group A	Developed rheumatic fever after leaving home	3,611
Group B	Did not develop rheumatic fever after leaving home	
	(1) Tuberculous cases at Corona Naval Hospital	519
	(2) Medical and surgical patients at Birmingham General Hospital	607
	(3) Intern and resident physicians at a civilian hospital	254

The question arose as to whether these individuals were likely to have been equally well informed concerning the occurrence of rheumatic fever in members of their families. It was suspected that individuals who had not had the disease themselves might be relatively uninformed in this respect in comparison with those who had developed the disease, unless the individual was himself a physician. On review of the data, this was found to be the case; nonmedical subjects who had never had the disease reported a significantly lower familial incidence than did physicians who had never had rheumatic fever. It was, therefore, necessary to exclude from this analysis of the effects of familial rheumatic fever all of those individuals who had not had the disease themselves and were not themselves physicians, the number of cases so excluded on the basis of inadequate information being 1,082. With respect to the influence of one attack of the disease upon the development of later attacks after leaving home, there was no reason to suppose that the knowledge of an earlier attack was less accurate in those who did not develop a later attack or more accurate in those who did; all 4,991 cases, therefore, were used in this analysis.

FINDINGS

In the "informed groups," as just defined, a study was made of the relationship between a positive family history of rheumatic fever and personal development of the disease while still in contact with the family. The results, in the form of a contingency table, are shown in Table II:

TABLE II. RELATIONSHIP BETWEEN FAMILY HISTORY AND PERSONAL ATTACK BEFORE LEAVING FAMILY

FAMILY HISTORY	PERSONAL HISTORY BEFORE SEPARATION FROM FAMILY	
	POSITIVE	NEGATIVE
Positive	369	258
Negative	551	2,731

These results could not possibly have been due solely to chance; there is, therefore, a definite tendency for the individual with a positive family history to develop the disease while still in contact with his family.

A study was made of the relationship between a positive family history and the personal development of the disease in the individual after separation from his family. The results, in the form of a contingency table, are shown in Table III.

TABLE III. RELATIONSHIP BETWEEN FAMILY HISTORY AND PERSONAL ATTACK AFTER LEAVING FAMILY

FAMILY HISTORY	PERSONAL HISTORY AFTER SEPARATION FROM FAMILY	
	POSITIVE	NEGATIVE
Positive	582	45
Negative	3,029	253

These results could easily have been due solely to chance; there is, therefore, no relationship between family history and the personal development of the disease after separation from the family. This same conclusion is reached when the cases are separately studied according to their own past personal histories.

From Tables II and III it is concluded that a positive family history is important only as long as the individual remains in contact with the family, and that a positive family history has no influence upon the risk of developing the disease after the individual leaves home.

It is now possible to study the role of a past personal history upon the risk of developing rheumatic fever without regard to family history. The reason for excluding the relatively "uninformed group" from such a study is now no longer present, since those who compose that group are presumed to be uninformed only in respect to the family history.

Table IV, therefore, includes all subjects studied and shows the relationship between personal past history of rheumatic fever and the later development of the disease.

TABLE IV. RELATIONSHIP BETWEEN PERSONAL PAST HISTORY OF RHEUMATIC FEVER AND THE LATER DEVELOPMENT OF THE DISEASE

PAST HISTORY OF RHEUMATIC FEVER	LATER DEVELOPMENT OF RHEUMATIC FEVER	
	YES	NO
Positive	861	59
Negative	2,750	1,321

This result could not have been due solely to chance; it is, therefore, clear that a positive personal history does tend to influence the later development of the disease.

Further study indicated that there was no significant difference in the incidence of a positive personal history between the three control groups composed of cases who did not develop rheumatic fever after separation from home; of the total 1,380 control cases, 2.9 per cent had a positive personal history. These data emphasize again the high frequency of rheumatic fever in the population, for nearly one in thirty-five of the young adults in the control groups had had this disease earlier in life.

SUMMARY

1. Three per cent of those making up the normal control groups had a personal history of rheumatic fever earlier in life.

2. An attack of rheumatic fever earlier in life tends to facilitate a later attack, but this difference is not great.

3. The occurrence of rheumatic fever in the family increases the risk of the individual developing the disease while still in contact with the family, but not after he is separated from the family. There does not, therefore, appear to be a strong and inherited susceptibility. The occurrence of multiple cases in families could be explained either on the basis of common environment or contagion. In the light of the widely accepted relationship of streptococcal infection to rheumatic fever, and the lack of agreement concerning the roles of social, economic, and geographic factors, we prefer to look on these data as indicating the dominant role of contagion in the development of rheumatic fever.

DIFFERENT MECHANISMS OF FUSION BEATS

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THE effect on the electrocardiogram of the simultaneous stimulation of a cardiac chamber by two impulses has been observed under various circumstances, and its experimental production has been used to clarify some of the fundamental problems of electrocardiography. Lewis and associates[1] arrived at an estimate of the duration of the impulse spread from the S-A node to the A-V node from the P-R interval of the beats with "transitional" auricular complexes, in a case in which the two pacemakers were competing. Wilson and Herrmann[2] in their experimental study of incomplete bundle branch block produced "combination complexes" by varying time relations of the normal levocardiogram and dextrocardiogram; their experiments led to the important conclusion that a delay in the passage of the impulse through one of the bundle divisions which amounts to more than three or four hundredths of a second (in the dog) will produce the same results in the electrocardiogram as complete division of one bundle branch. Furthermore, they observed the occurrence of a number of varying ventricular complexes after cutting both bundle branches, and attributed this phenomenon to the simultaneous activity of two ventricular pacemakers; they concluded that complete bundle branch block in man, associated with ventricular complexes of varying form, was usually due to bilateral bundle branch block, and was not due to a lesion of the main stem of the A-V bundle. This was later confirmed in an autopsied case reported by Don, Grant, and Camp.[3] Recently, Butterworth and Poindexter,[4,5] by using an abnormal electric conducting pathway in the dog and in the cat, produced electrocardiograms closely resembling those seen in patients with the Wolff-Parkinson-White syndrome; they concluded that the abnormal ventricular complexes were "fusion beats"[6,7] due to the fusion within the ventricles of the sinus impulse conducted both via the usual pathway and via a faster conducting accessory pathway. It has been recognized that several mechanisms can cause fusion beats. The material presented in this paper was collected in order to illustrate the various mechanisms responsible for fusion beats as they are encountered in clinical electrocardiography.

From the Cardiovascular Department of Michael Reese Hospital, Chicago.
Aided by the Herbert G. Mayer Fund for Cardiovascular Research.
The department is supported in part by the Michael Reese Research Foundation.
Received for publication April 16, 1947.
Presented at the Inter-American Congress of Cardiology, Mexico D. F., Oct. 5-12, 1946.
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TABLE I. CLASSIFICATION OF FUSION BEATS

FUSION BEATS	Impulses of different origin	Fusion in the auricles	Sinus impulse plus retrograde impulse of	Nodal origin	Premature systoles (Figs. 1, *A* and *B*, and 2)
					Escapes in: Sinus bradycardia; S-A block (Fig. 3); 2nd degree A-V block
				Ventricular origin	Idioventricular beats in: Complete A-V block (Fig. 1, *C*)
			Sinus impulse plus auricular premature systole		
			Auricular premature systoles from two or more different origins		
		Fusion in the ventricles	1. Supraventricular impulse originating from		Sinus node (Figs. 4 and 5, *B*); Auricular ectopic focus; A-V node; Flutter; Fibrillation (Fig. 5, *A*)
			plus		
			Idioventricular beat consisting of		Premature systoles (Figs. 4 and 5, *A*), or tachycardia with A-V dissociation (Fig. 5, *B*); Escape
			2. Sinus impulse plus A-V nodal beat		In A-V dissociation with aberrant conduction of nodal beats; In A-V dissociation in Wolff-Parkinson-White syndrome (Fig. 7)
			3. Two impulses of ventricular origin		Two idioventricular pacemakers in complete A-V block (Fig. 6); Ventricular premature systoles from two or more foci
	Impulse of a single origin	Fusion in the auricles	Reciprocal beats of sinus origin		
		Fusion in the ventricles	Reciprocal beats of A-V nodal or idioventricular origin (Fig. 2)		Of sinus origin when QRS is less than 0.12 second. Wider QRS may also indicate fusion (Fig. 7)
			Wolff-Parkinson-White syndrome		In auricular fibrillation (Fig. 5, *C*)

VARIETIES OF FUSION BEATS

A classification of fusion beats is presented in Table I. Fusion beats can be classified according to two criteria: (a) the origin of the fusing impulses, and (b) the site of the fusion. Since the fusing impulses can be of either different or identical origin, and since fusion which is reflected in the electrocardiogram can take place either in the auricles or in the ventricles, four different types of fusion beats can be distinguished.

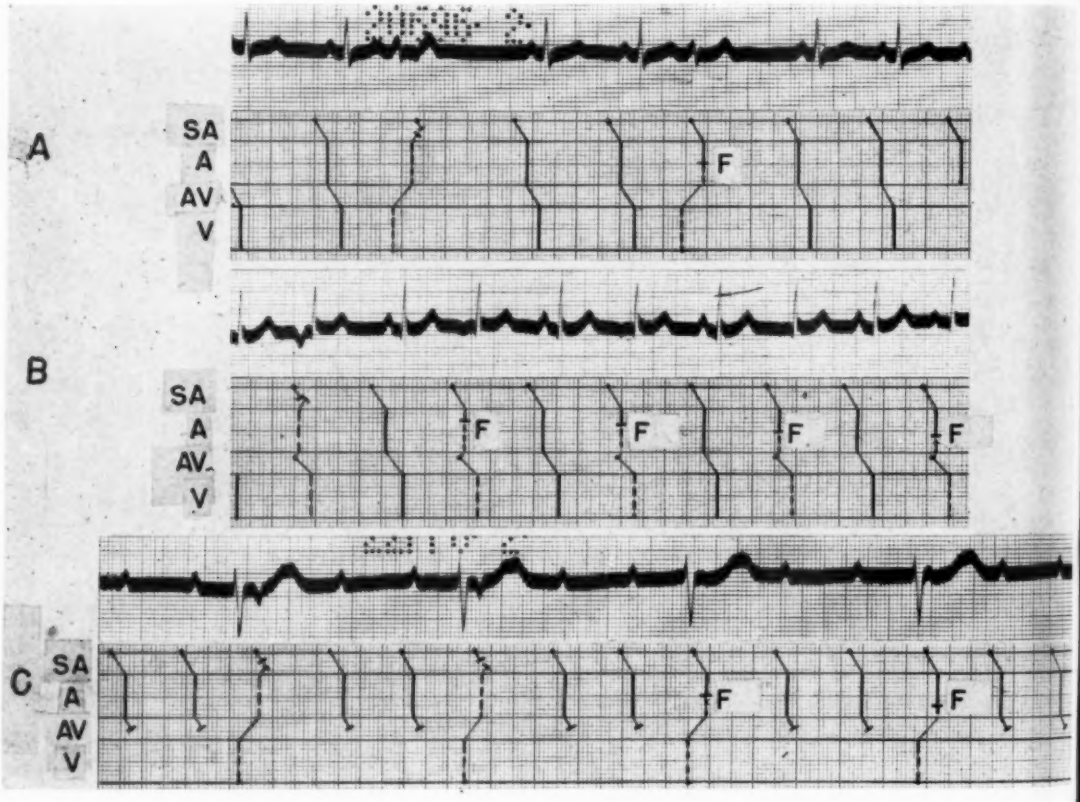

Fig. 1.—Three examples of auricular fusion beats. *A*, Fusion of the retrograde impulse of a ventricular premature systole with the sinus impulse (*F*). After the second ventricular premature systole, no sinus P wave is inscribed nor is there any retrograde P. *B*, Different degrees of fusion (*F*) between the retrograde impulse of nodal premature systoles and sinus impulses. The P waves show transition from the deeply inverted retrograde P (first beat) to the tall upright sinus P wave. The shortened P-R of the premature beats and the fixed coupling speak for this interpretation and tend to rule out the occurrence of multiple auricular premature systoles from different foci. *C*, Fusion of the retrograde impulse of an idioventricular beat with the sinus P in a case of complete A-V block with preserved retrograde conduction. The P waves following the third and fourth idioventricular QRS have an intermediate contour between the retrograde and the sinus P, and they occur at a time when both the sinus P and the retrograde P can be expected.

The mechanism in each case of this and subsequent figures is illustrated in the diagram below the electrocardiogram. The conventions are those used customarily. S-A indicates the impulse spread between the sinus node and the auricles. A-V represents the spread of the impulse through the A-V junction between the auricle (*A*) and the ventricle (*V*). Sinus impulses are indicated by solid lines. Ectopic impulses by dash lines. *F* indicates a fusion beat. Variations in its location are represented by varying the level at which the two vertical lines meet. Block and interference are indicated by short lines at right angles to the lines representing the impulse spread.

(*A*) *Fusion of Impulses of Different Origin.*—

(1) *Auricular Fusion Beats*: Such fusion beats are due to the sinus impulse fusing with the retrograde impulse of an A-V nodal or idioventricular beat; the latter may be either a premature systole (Figs. 1, *A* and *B*, and 2) or an escape occurring during the ventricular pause caused by marked sinus bradycardia, S-A block (Fig. 3), or A-V block (Fig. 1,*C*). It is rare to find auricular fusion beats resulting from the fusion of the sinus impulse with that of an auricular premature systole[8] or from fusion of two auricular premature systoles.

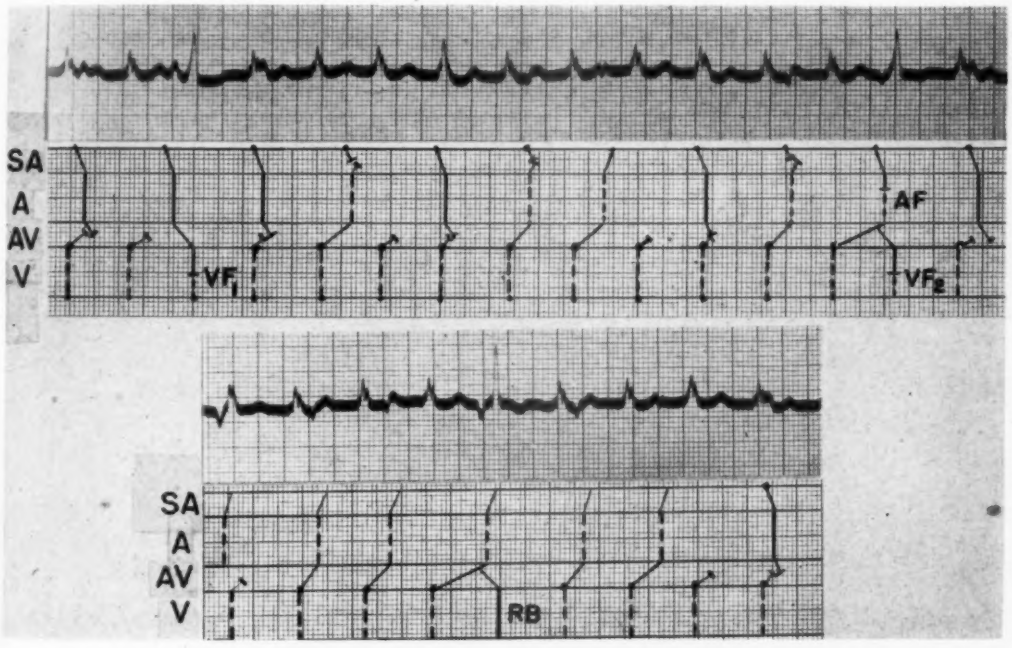

Fig. 2.—Two portions of the same record (Lead II) showing auricular and ventricular fusion beats in a case of ventricular paroxysmal tachycardia with retrograde conduction, retrograde block exhibiting the Wenckebach phenomenon, and reciprocal beats. Three types of P waves are seen: (a) upright sinus P waves, (b) deeply inverted (retrograde) P waves, and (c) a fusion P wave (*AF*) with an intermediate contour between (a) and (b), and occurring at the time when a sinus P wave was expected. Note that in the second strip only one sinus P is seen, due to the fact that the sinus rate is slower than in the first strip and most retrograde impulses reach and discharge the sinus pacemaker.

In addition, three types of ventricular complexes are seen: (a) A broad, notched QRS of idioventricular origin occurring at a rate of about 120 per minute and with slightly varying contour due to the superimposition of sinus P waves. (b) One beat has a normal QRS duration preceded by a retrograde P and representing a reciprocal beat (*RB*). (The forward conduction of this beat and of a later such beat is represented by solid lines.) (c) Two ventricular complexes show intermediate contour between (a) and (b). The first one (VF_1) is the result of fusion of impulses from the sinus and from the idioventricular pacemakers. The second one (VF_2) results from the fusion of two impulses of identical origin; the reciprocal impulse invades the ventricle simultaneously with the next idioventricular impulse. Note that this latter follows an auricular fusion beat, thus suggesting that re-entry occurs below the auricles.

The preceding explanation was arrived at and is substantiated by the analysis of several long strips obtained on the same patient.

Conventions as in Fig. 1.

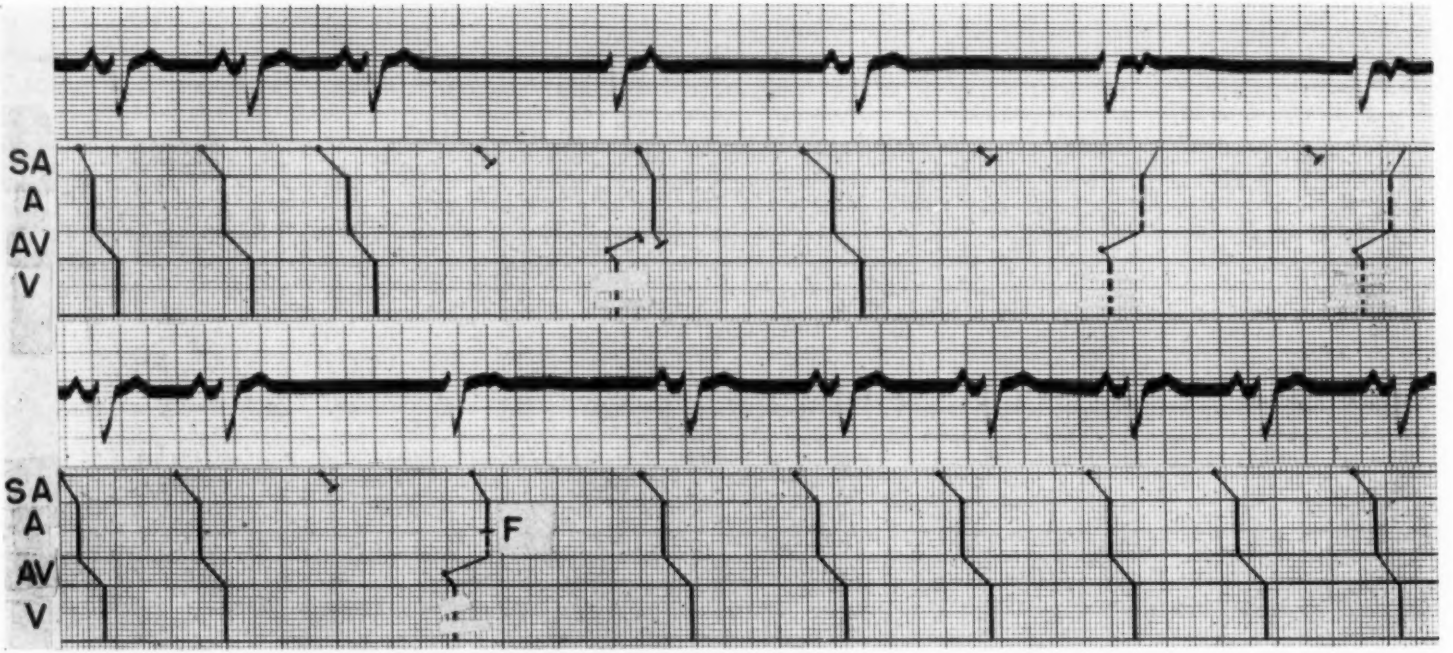

Fig. 3.—Two portions of the same Lead II showing an auricular fusion beat occurring in a case of S-A block with nodal escapes followed by retrograde P waves. The fusion beat (*F*), shown in the lower strip, is intermediate in contour between the retrograde and the sinus P. Note that the interval between the fourth and fifth sinus P in the upper strip is almost identical with the interval between the fusion beat and the following sinus P, confirming that a sinus P was inscribed during *F*. The R-P interval of the fusion P is similar to that of the last two beats in the upper strip.

Conventions as in Fig. 1.

(2) *Ventricular Fusion Beats*: Such fusion beats result from fusion of a supraventricular impulse with a ventricular premature systole or a ventricular escape; the supraventricular impulse may be sinus (Figs. 2, 4, and 5, *B*), auricular, or A-V nodal in origin, or it may be the impulse of auricular fibrillation (Fig. 5*A*) or auricular flutter. Fusion beats with varying time relations between the supraventricular impulse and the premature impulse of a single ectopic focus

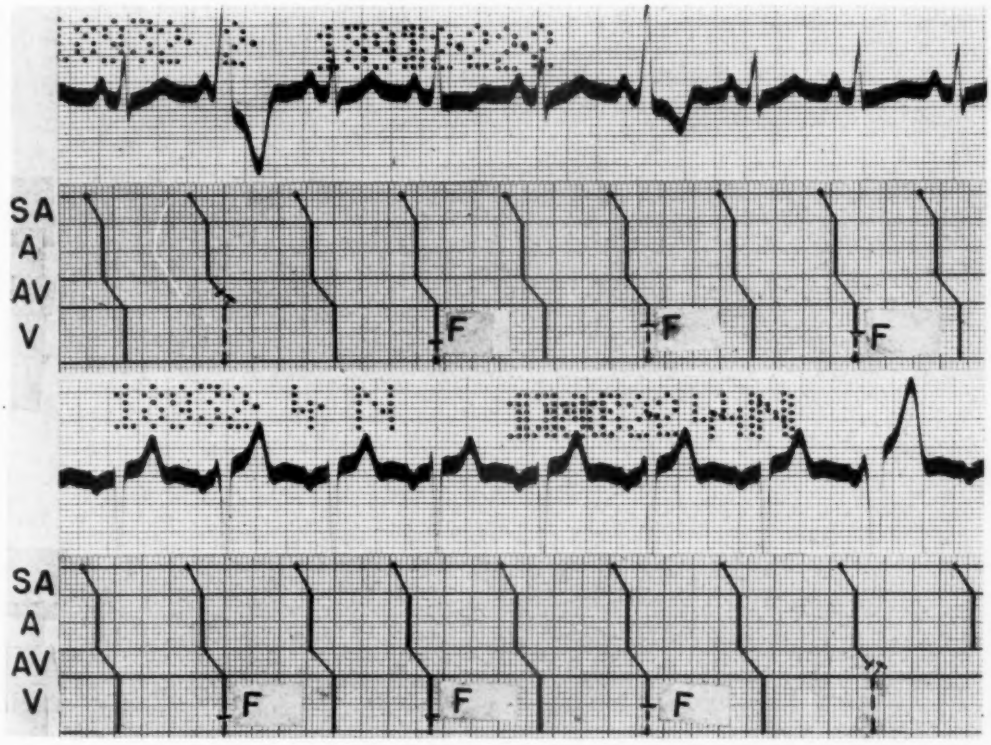

Fig. 4.—Leads II and CF_2 of the same patient showing fusion (*F*) of sinus impulses and late ventricular premature systoles in a case of parasystole. The difference in contour of the several ventricular fusion beats indicates variations in the fusion. It is apparent that the closer the P-R approaches the sinus P-R, the larger is the share of the ventricles controlled by the sinus impulse, as evidenced by its greater approximation to the sinus contour.

Conventions as in Fig. 1.

may lead to the erroneous diagnosis of premature systoles from multiple foci if the mechanism of fusion is not recognized; this is especially likely to occur in cases with auricular fibrillation (Fig. 5, *A*). In cases of A-V dissociation and aberrant conduction of the nodal beats, ventricular complexes can be found intermediate in contour between that of the sinus and nodal beats which occur at a time when fusion of the two impulses is to be expected. In cases of Wolff-Parkinson-White syndrome presenting A-V nodal escapes, supraventricular impulses conducted via the accessory pathway may fuse with the nodal impulses conducted via bundle of His and give rise to a transitional form of the ventricular

complex (Fig. 7) (Rosenbaum and associates,[9] and Ohnell[10]). This is true both for cases with sinus rhythm and for those with auricular fibrillation; it could also occur in the presence of nodal premature systoles. Finally, ventricular fusion beats occur as a result of simultaneous stimulation by two idioventricular impulses, as seen in cases of complete A-V block with two competing idioventricular pacemakers (Fig. 6). Similar fusion may occur in the presence of ventricular premature systoles from multiple foci; however, its recognition is difficult unless both are parasystolic in origin.

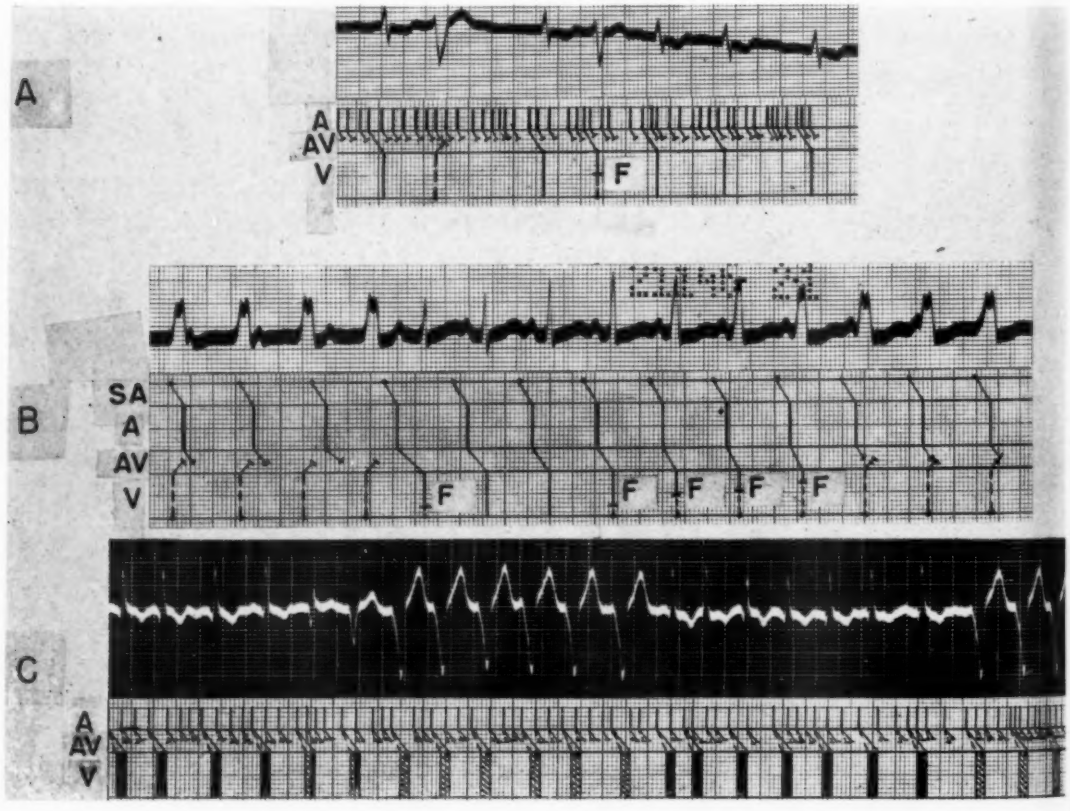

Fig. 5.—*A*, Ventricular fusion beat in a case of auricular fibrillation. Fusion occurs between the supraventricular impulse and a ventricular premature systole. This is evidenced by the identical coupling of the ventricular premature systole and the fusion beat as well as by the intermediate contour of the latter. *B*, Varying location of fusion in a case of ventricular paroxysmal tachycardia with A-V dissociation. The gradual transition in contour of the ventricular complexes is explained by the small difference in rate between the slower sinus and the faster ventricular pacemaker. (This record was obtained on the patient shown in Fig. 2, on an occasion when no retrograde conduction from the ventricular pacemaker was present.) *C*, Ventricular fusion beats in a case of Wolff-Parkinson-White syndrome with auricular fibrillation. The wide QRS complexes are identical with those found during sinus rhythm showing short P-R and prolonged QRS (not illustrated). The fifth and sixth beats show a gradual transition from the narrow to the wide QRS, indicating the simultaneous invasion of the ventricles by a supraventricular impulse over both the bundle of His and accessory pathway. The difference in contour between these beats indicates an increasing share of the control of the ventricles by way of the accessory bundle.

Conventions as in Fig. 1, but in *C*, the solid rectangles indicate stimulation of the ventricles via the bundle of His. The shaded portion represents stimulation via an accessory bundle. The spread over the two pathways is indicated by the double oblique lines in A-V.

(*B*) *Fusion of Impulses of Identical Origin.*—Such fusion beats could occur in A-V block with re-entry and when the impulse spreads along a double pathway.

(1) *Auricular Fusion Beats*: No such fusion beats were encountered in our material; however, in a case reported in the literature,[11] the conditions which could give rise to such fusion beats were present. The case presents the unique picture of sinus rhythm with 2:1 A-V block and re-entry of the sinus impulse

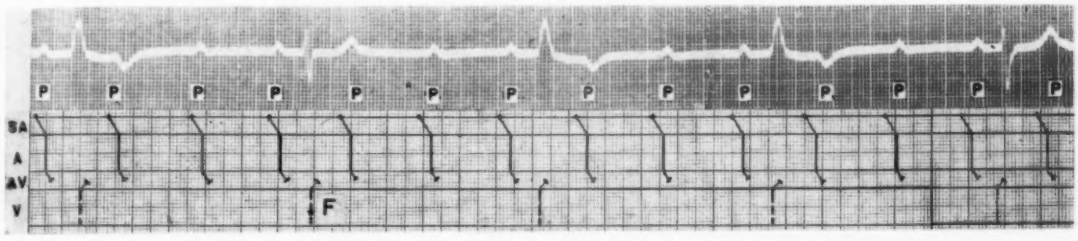

Fig. 6.—A ventricular fusion beat in a case of complete A-V block with two idioventricular pacemakers located presumably one in each ventricle. The second ventricular beat shows an intermediate form between the two, and its QRS is narrower. Longer records show that both pacemakers have an irregular and similar rate.

Conventions as in Fig. 1, except that the second idioventricular pacemaker is represented by a dotted line.

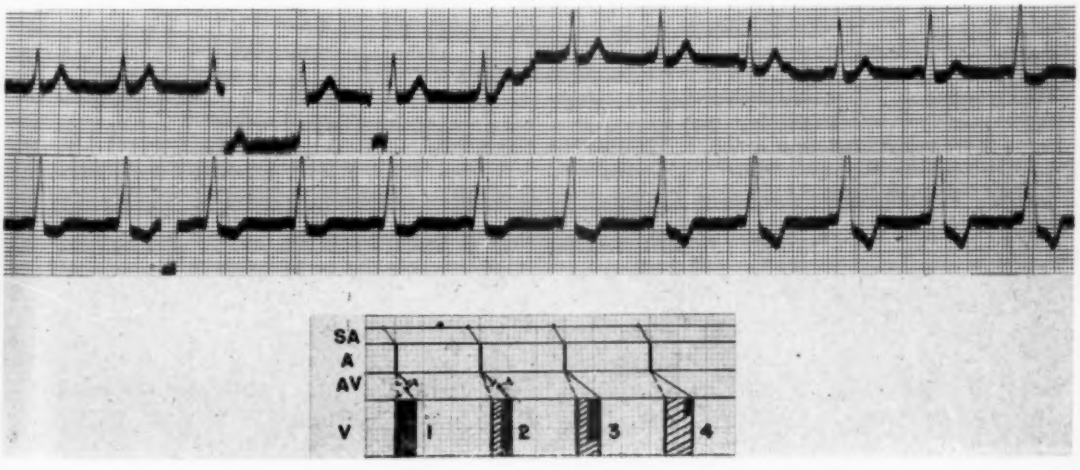

Fig. 7.—Ventricular fusion beats in a case of Wolff-Parkinson-White syndrome with transitory A-V dissociation after 1/100 grain of atropine sulfate intravenously. Continuous record, the last beat of the upper strip is repeated at the beginning of the lower strip. The first four beats of the upper strip show A-V nodal rhythm with QRS of normal duration (Diagram 1). Starting with the fifth beat a P wave appears in front of QRS and the P-R lengthens gradually to 0.10 second, QRS gradually becomes wider with slurring of its initial portion, and R becomes taller, S-T becomes depressed, and T inverted (Diagram 2). It is possible that the contour changes in the second strip are no longer associated with escape of the nodal pacemaker. The whole heart may now be under the control of the S-A node, partly via the accessory bundle and partly via the bundle of His. However, the site of fusion of the impulse conducted over the normal pathway with that conducted along the accessory bundle varies as the effect of atropine on the conduction through the A-V node disappears (Diagrams 3 and 4). Nevertheless, it cannot be ruled out that the transitional contour in the first portion of the lower strip still reflects the interplay of the two pacemakers.

Conventions as in Fig. 5, *C*.

giving rise to reciprocal auricular beats; fusion in the auricles of the reciprocal impulse with the next sinus impulse would result in a fusion beat.

(2) *Ventricular Fusion Beats*: Such beats occur in cases of ventricular rhythm associated with reciprocal beats, the fusion being between the reciprocal and the next automatic beat (Fig. 2). In A-V nodal rhythm with reciprocal beats, such fusion beats can be diagnosed only when the reciprocal or nodal beat shows aberrant conduction. Another type of ventricular fusion beat is due to spread of the supraventricular impulse along both the normal A-V bundle and an accessory A-V bundle, as present in cases with the Wolff-Parkinson-White syndrome. Whether all the beats in such cases with sinus rhythm, short P-R, and prolonged QRS are actually fusion beats cannot be answered. Uniformity and lack of transitional complexes would seem to indicate that the difference of the conduction times of the two pathways is of such duration that the impulse conducted through the accessory bundle stimulates both ventricles before the impulse can reach the ventricles via the slower A-V conducting path. However, the fact that the sum of the P-R and QRS intervals remains constant in records showing both normal P-R with normal QRS and shortened P-R with prolonged QRS suggests that the last portion of the wide QRS may be due to stimulation by the impulse conducted along the normal pathway. This is undoubtedly true in the cases of Wolff-Parkinson-White syndrome without abnormal QRS prolongation but with the typical notching of the first portion of QRS (Fox,[12] Öhnell,[10] and Katz, Langendorf, Mintz, and Malinow[13]); whenever the value representing the difference in A-V conduction time along the two pathways is within a critical range, any procedure (like carotid sinus pressure) or medication (like atropine) that changes vagal tone and with it the conduction delay of the impulse spreading normally through the A-V node will shift the site of fusion and influence the duration of QRS and the contour of its second portion (Fig. 7). In the combination of auricular fibrillation and the Wolff-Parkinson-White syndrome (Langendorf[14]) ventricular fusion beats are to be expected with varying time relations between the supraventricular impulses conducted along the two pathways: this actually can be demonstrated (Fig. 5, *C*).

Most fusion beats are premature. In the commonest form of fusion, a ventricular premature impulse fuses with a sinus impulse, thus abbreviating the P-R interval. This shortening may amount to as much as 0.06 second in the human heart (Ashman and Hull[15]), indicating that the conduction from the ectopic focus to the bifurcation of the common bundle may require as much as 0.06 second. As was demonstrated in animal experiments,[2] such shortening of the P-R of a fusion beat can be absent in a case of bundle branch block where the sinus impulse fuses with an impulse originating in the ventricle affected by the bundle branch block.

SUMMARY

(1) A review is presented of the contributions to the understanding of the normal and abnormal spread of the cardiac impulse, which have been revealed by the study of fusion beats (transtitional complexes, combination complexes) in the electrocardiogram.

(2) A classification of fusion beats is given, based on two criteria: origin of the fusing impulses and site of fusion.

(3) The various mechanisms reflected in the electrocardiogram exhibiting fusion beats are discussed and illustrated.

(4) A case of Wolff-Parkinson-White syndrome with auricular fibrillation, showing complexes with a transitional contour (fusion beats), is presented as new evidence to demonstrate the functioning of both the normal, and an accessory, pathway in the Wolff-Parkinson-White syndrome.

We are indebted to Dr. L. N. Katz for his valuable suggestions.

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GLOSSOPHARYNGEAL NEURALGIA: A CAUSE OF CARDIAC ARREST

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GLOSSOPHARYNGEAL tic douloureux or neuralgia is a comparatively rare but well-recognized syndrome. In respect to the stabbing paroxysmal nature of the pain and its relation to specific trigger zones, it is exactly comparable to the commoner trigeminal tic douloureux. In neurosurgical clinics the two types of neuralgia occur in a ratio of about one to forty.

The significance of cardiac arrest and syncope associated with glossopharyngeal neuralgia was first emphasized by Riley and associates,[1] in a brief report of two cases in 1942. This report called attention to the afferent pathway of the carotid sinus reflex through the glossopharyngeal nerve and suggested the correlation of the simultaneous neuralgia and excessive stimuli to the sinus reflex. Neither of the two cases was reported to have been subjected to operation. Since then, no other reports of similar cases have come to light in medical literature. However, one of us (Ray) had the opportunity of examining such a case with Dr. Jefferson Browder in 1943 and this patient was relieved of all symptoms by intracranial section of the glossopharyngeal nerve.

Because of the importance of further establishing the authenticity of the syndrome and calling wider attention to the importance of its recognition, there is justification for reporting another comparable case.

CASE REPORT

History.—E. L., a 49-year-old Parisian man, was admitted to the New York Hospital in June, 1946, complaining of recurring severe pain in the left side of the base of the tongue, pharynx, and neck, accompanied by fainting. He had first experienced the pain three years before when he suffered from an infection in the left tonsillar region said to have been a peritonsillar abscess. As soon as the infection had subsided a tonsillectomy was performed and the initial pain subsided after several weeks, but every few months, thereafter, he was troubled by stabs of pain in the left tonsillar region. In March, 1946, with a recurrence of pain, another operation for removal of tonsillar tissue failed to provide relief. Instead, the pain increased and for two weeks prior to admission to the hospital, it had been so severe that the patient was confined to bed. Only moderate relief had been obtained from the regular administration of morphine.

The pain was of an intense piercing quality, beginning in the base of the tongue and tonsillar region on the left side and spreading deeply in the neck just below and behind the angle of the jaw, thence deeply into the ear on the same side. A rapid succession of lightninglike stabs would continue for five to forty-five seconds, then subside as suddenly as they had appeared. Paroxysms

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Received for publication April 24, 1947.

recurred every several minutes during waking hours, the longest period of freedom being about ten minutes. The pain was induced by swallowing and talking so that he ate and drank very little and conversed by signs and writing.

In the more severe attacks, he felt faint and sometimes lost consciousness. Since he was under the impression that he had a "weak heart" as a result of having been exposed to gas in World War I, he feared that his heart might be failing and that death was impending.

Examination.—The general physical examination revealed nothing remarkable except for moderate obesity and dehydration. The tongue, tonsillar fossae, and pharynx were normal in appearance, the neck contained no masses, and otoscopic examination was negative. The cardiac sounds, rhythm, and size, as well as the electrocardiogram, were normal. However, the cardiac rate varied between 16 and 90 beats per minute and averaged about 65. The blood pressure averaged 90/60. The temperature and respiratory rates were normal. Urinalysis, blood counts, and blood Wassermann were all negative.

Description of Attacks.—Many attacks were observed and, with all of those in which the pain was more than a fleeting stab, there was simultaneous slowing of the pulse rate for a few seconds. With the more intense and longer lasting paroxysms, there occurred asystole for several seconds followed by bradycardia and by a fall in systolic blood pressure of 25 to 30 mm. Hg for the duration of the pain.

In the more severe attacks in which there was cardiac arrest and fall in blood pressure, the patient would become pale, lose visual fixation, show signs of confusion, and, occasionally, of complete syncope. Recovery from syncope was simultaneous with the return of normal cardiac rate and rhythm and with cessation of pain.

Electrocardiographic Record During an Attack.—During a control record (Fig. 1, *A*) the rate was 58 per minute. The patient was then induced to take a single swallow of cold water while Lead II of the electrocardiogram was being taken. This was followed immediately by the usual pain and dizziness. The electrocardiogram showed marked slowing of the heart rate with sinus bradycardia (16 per minute), then asystole for 3.8 seconds (Fig. 1, *B*). At the end of this interval there was ventricular escape, followed by retrograde conduction with an auricular premature contraction and then another ventricular escape, after which there was reversion to normal rhythm. The return to normal rhythm and a more rapid rate, 50 per minute, was accompanied by recovery of the patient from dizziness.

Cocainization of the posterior portion of the tongue and the pharynx diminished the degree of the pain but did not abolish it. Pressure on the neck over the region of the left carotid sinus induced the pain and was so poorly tolerated that it was not possible to determine the sensitivity of the left carotid sinus by pressure. Pressure over the right carotid sinus was painless and unaccompanied by any alteration in cardiac rate or blood pressure. Unfortunately, the extreme discomfort and apprehension of the patient prevented the employment of other tests which would have been instructive but unnecessary.

The *diagnosis* was left glossopharyngeal tic douloureux associated with an increased carotid sinus reflex.

Operation.—Intratracheal ether anesthesia was administered and a left suboccipital craniotomy performed. The left cerebellar hemisphere was uncovered and retracted medially to expose the region of the jugular foramen. The glossopharyngeal nerve was isolated from the adjacent vagus nerve and divided. The blood pressure, up to the time of dividing the nerve, had been steadily 130/85 but immediately following the division, the pressure rose precipitiously to 190/115; the cardiac rate at the same time increased from 80 to 105.

Postoperative Course.—On the awakening of the patient from the anesthetic, the former pain was gone and has not returned (six months' follow-up). Recovery from the operation was prompt and uncomplicated so that he was able to leave the hospital in ten days.

Within six hours after operation the blood pressure and cardiac rate had returned to the approximate levels where they remained thereafter (blood pressure 140/80, and cardiac rate, 80).

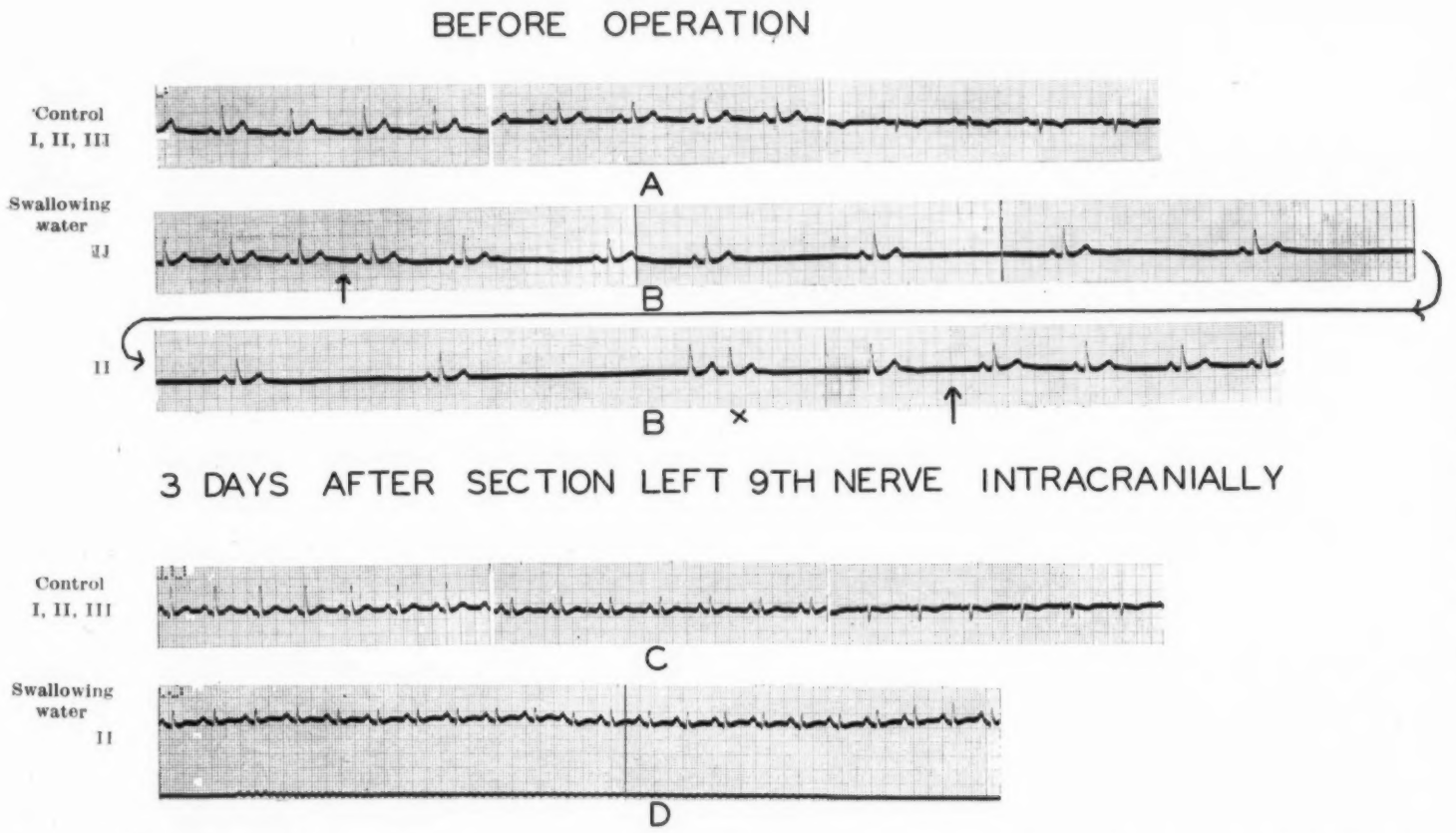

Fig. 1.—*A* and *B* show electrocardiographic observations made before section of the left ninth nerve intracranially. *A* shows the three standard leads of the patient's electrocar liogram as a control taken on June 21, 1946. *B* shows a long strip of Lead II of the electrocardiogram taken immediately after *A* to show the effect of taking a swallow of water. The first arrow indicates the time at which the patient swallowed and the second one when he finished. There was marked slowing of the heart with sinus bradycardia following by asystole for 3.8 seconds, with ventricular escape the beat before *X*. This was followed by retrograde conduction with a premature contraction (*X*) and then another ventricular escape, after which there was return to normal rhythm when swallowing had been completed. Swallowing was associated with pain, and asystole with dizziness. *C* and *D* show electrocardiographic observations which were made three days after the left ninth nerve had been sectioned intracranially on June 21, 1946. *C* shows the three standard leads taken on June 24, 1946, and serve as a control. *D* shows Lead II of the electrocardiogram made immediately after *C* to illustrate the effect of swallowing. The signal at the bottom indicates when swallowing started and ended. There was no change in heart rate.

There was anesthesia of the base of the tongue, palate, and pharynx on the left in the region supplied by the glossopharyngeal nerve. The patient was unaware of this sensory loss. Pressure over the carotid sinus caused no symptoms and no alteration in blood pressure or cardiac rhythm. The form of the postoperative electrocardiogram was normal, though by comparison with the preoperative electrocardiogram there were minor changes compatible with the differences in the preoperative and postoperative blood pressures. The rate was more rapid, 87 per minute (Fig. 1, *C*). Three days after section of the left ninth nerve intracranially, swallowing was not accompanied by any change in the heart rate (Fig. 1, *D*) and he experienced no symptoms.

DISCUSSION

The nature and distribution of the pain in this patient leaves no doubt that the condition was glossopharyngeal neuralgia. It is not possible to evaluate the role of the reported quinsy that preceded the onset of the pain, but the history of tonsillar inflammation is obtained in an impressive number of those who develop glossopharyngeal neuralgia. It may be that some have had unrecognized herpes zoster of the ninth nerve but more important, perhaps, is the observation that tonsillectomy is of no aid in controlling the pain and, as in this case, cocainization of the glossopharyngeal areas supplied by the nerve cannot be expected always to abolish the pain even temporarily.

It was impossible to test the sensitivity of the left carotid sinus by pressure without inducing the pain and its accompanying alteration in cardiovascular functions. However, the absence of a hypersensitive right carotid sinus and of generalized vascular disease so commonly seen in patients with carotid sinus syncope suggests that the left carotid sinus was not hypersensitive. Thus, the cardiac arrest and fall in blood pressure may be assumed to have resulted somehow from overactivation of the afferent carotid sinus impulses traversing the glossopharyngeal nerve by a barrage of pain impulses traversing the same nerve. In some patients with hypersensitive carotid sinus reflex, there exists a dull pain which has the quality of carotidynia and both conditions appear to result from sclerotic alterations of the arterial walls; this condition is not comparable to the syndrome under discussion.

The cardiac rate and blood pressure are controlled in part by autonomic centers in the medulla whose tone is regulated by numerous afferent impulses from the body, the most important of which, perhaps, are those from the carotid sinuses. The complete afferent pathway of impulses from the carotid sinuses in man is not fully known. However, the pressure component of the reflex is mediated wholly by the glossopharyngeal nerve, as evidenced by the fact that intracranial division of this nerve abolishes all effects of digital compression of the carotid sinus in patients known to have a hypersensitive sinus.[2] The temporary rise in blood pressure and cardiac rate after division of the glossopharyngeal nerve intracranially is due to interruption of afferent carotid sinus impulses which exert an inhibitory effect on central autonomic centers.

In patients with the hypersensitive carotid sinus syndrome of the "vagal type," in which there is cardiac arrest and resulting fall in blood pressure, atropinization will abolish the effects of compression of the sensitive sinus. In this patient it is likely that atropinization would have done away with the cardiac

arrest and its associated fall in blood pressure and syncope, though it could hardly have been expected to alter the pain. The test was not used because of the patient's impatience with any delay in the operation to relieve his pain. Atropinization would undoubtedly be useful in excluding the cardiac effects of the syndrome during the period before a delayed operation. It would also have been interesting to observe the effects of procainization of the carotid sinus on the side of the pain, though there may possibly have been no effect.

CONCLUSIONS

1. Glossopharyngeal neuralgia may be accompanied by cardiac arrest with syncope.

2. This effect is mediated through the carotid sinus reflex mechanism.

3. Section of the ninth nerve intracranially on the affected side affords relief from the neuralgia and abolishes the episodes of cardiac arrest with syncope.

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THE DIMINISHED EFFICIENCY AND ALTERED DYNAMICS OF RESPIRATION IN EXPERIMENTAL PULMONARY CONGESTION

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INTRODUCTION

QUANTITATIVE measurements of the relative efficiency of respiration in the normal lung, as contrasted with the congested lung, have not been made in the intact experimental animal. In 1934 Christie and Meakins,[1] utilizing simultaneous determinations of dynamic intrapleural pressure and of tidal exchange in patients with congestive heart failure, demonstrated a marked decrease in pulmonary distensibility. With appropriate treatment, distensibility was found to increase as the patient improved. In the present study, an approach similar to that of these authors has been used, and studies of the efficiency of respiration have been made on normal dogs at rest and during hyperpnea (produced by the inhalation of carbon dioxide) and contrasted with the relative efficiency of respiration after pulmonary congestion induced by rapid venous infusion. With this approach, a quantitative comparison of the work necessary to achieve a given amount of tidal exchange has been possible in an animal with normal lungs and in the same animal after severe pulmonary congestion. From measurements of tidal exchange, ventilation, and intrapleural pressure fluctuations, a representation of the dynamic changes in these factors during progressive pulmonary congestion has been obtained.

PROCEDURE

Dogs were anesthetized by sodium pentobarbital (.0264 Gm. per kilogram of body weight) administered intravenously. A tracheal cannula was inserted and connected with a Benedict-Roth type spirometer, the calibrated movements of which were recorded by a pointer upon smoked paper, providing a measure of tidal exchange. Ventilation per minute was obtained by multiplying the average tidal exchange by the respiratory rate. Surface area was calculated from the Meeh-Rubner formula,[2] and the tidal exchange (in cubic centimeters) and ventilation (in liters per minute) were expressed per square meter of surface area. Intrapleural pressures were measured by inserting the tips of small rubber catheters (provided with lateral apertures) about three-eighths of an inch into the pleural space, by means of a small hemostat. A previously placed purse-string suture was immediately drawn airtight about the catheter. A water manometer with conduction tubing of 5 mm. bore was utilized to measure variations in intrapleural pressure. The suitability of such an instrument for recording quantitative measurements of intrapleural pressure has been shown by Christie and McIntosh.[2a]

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Received for publication March 25, 1947.
*Work done during the tenure of a Life Insurance Medical Research Student Fellowship.

The spirometer was filled with (1) 100 per cent oxygen for experiments at rest and during congestion; and (2) with a mixture of 5 per cent carbon dioxide and 95 per cent oxygen to determine the effect of carbon dioxide. Before the administration of carbon dioxide the soda lime was removed from the spirometer, so that rebreathing caused a progressive increase in the carbon dioxide content of the inspired air, producing a maximal degree of stimulation. Venous pressures were measured from the external jugular vein (using a small amount of heparin in the manometer) with the animal's back (supine position) as a reference point. Pulmonary congestion was produced by the intravenous administration of (a) 0.9 per cent sodium chloride solution; (b) solutions containing 5 Gm. of sodium bicarbonate plus 5.55 Gm. of sodium chloride per liter; and (c) solutions containing 1.25 Gm. of sodium bicarbonate plus 7.30 Gm. of sodium chloride per liter. The rates of fluid administration varied in different animals from 5.0 to 30.0 c.c. per kilo per minute. The total amount of fluid administered varied between 2.0 and 4.0 liters per animal. Nineteen dogs were utilized. The pH of the blood was determined by means of the Coleman electrometer, using a glass electrode. Oxygen content and capacity of whole blood and the carbon dioxide content of serum were determined by the methods of Van Slyke and Neill,[3] carbon dioxide tension being calculated by using the Henderson-Hesselbach equation.

RESULTS

Effects of Rapid Venous Infusion.—The rapid infusion produced abrupt increases in venous pressure, which eventually rose to 500 mm. of saline or above (Table I) in most animals. Observation of the exposed cervical veins revealed that they became markedly distended during the first few minutes of the administration of fluid. The respiratory rate rose moderately, and participation of the accessory muscles of respiration, especially of the expiratory group, became progressively more marked during each experiment. In most animals the respiratory rate slowed somewhat as pulmonary congestion became very severe, and respiration became very labored. If the infusion was continued when this state was reached the animals expired very shortly. Each animal was examined after death and the lungs were universally found to be heavy, reddened, and leathery, and fluid was expressed profusely from the congested cut surface of the lungs. The liver was found to be large, reddened, and the cut surface revealed evidence of marked congestion. The heart was usually slightly dilated.

TABLE I. JUGULAR VENOUS PRESSURES (IN MM. H_2O).

DOG NO.	BEFORE INFUSION	DURING MAXIMUM PULMONARY CONGESTION
20	140	585
21	100	600
22	66	615
25	119	560
26	95	235+
27	160	510
28	85	540
30	84	540
31	105	485
32	100	520
33	87	560
34	160	450
35	85	500
36	90	600

Alterations in Intrapleural Pressure.—The maximum intrapleural pressure during expiration, before the administration of fluid or carbon dioxide, was found to be negative in eighteen of the nineteen animals (Table II), usually varying from −1.0 to −4.6 cm. of water. In the remaining animal the expiratory intrapleural pressure was at the atmospheric level, but in no instance was the expiratory intrapleural pressure at rest above atmospheric pressure. During inspiration the total intrapleural pressure fluctuations during quiet breathing in the different animals, with a few exceptions, ranged between −4.0 and −10.0 cm. of water. After the inhalation of the carbon dioxide-oxygen mixture the total intrapleural pressure fluctuations increased markedly in each animal (Table II), usually remaining below atmospheric pressure. In only three of the eight animals given carbon dioxide did the expiratory intrapleural pressure rise above the atmospheric level.

By contrast with the resting state, and with most of the experiments in which respiration was stimulated by carbon dioxide, the expiratory intrapleural pressure rose well above atmospheric pressure in every animal in which pulmonary congestion was produced (Table II and Fig. 1). In seventeen of the nineteen animals

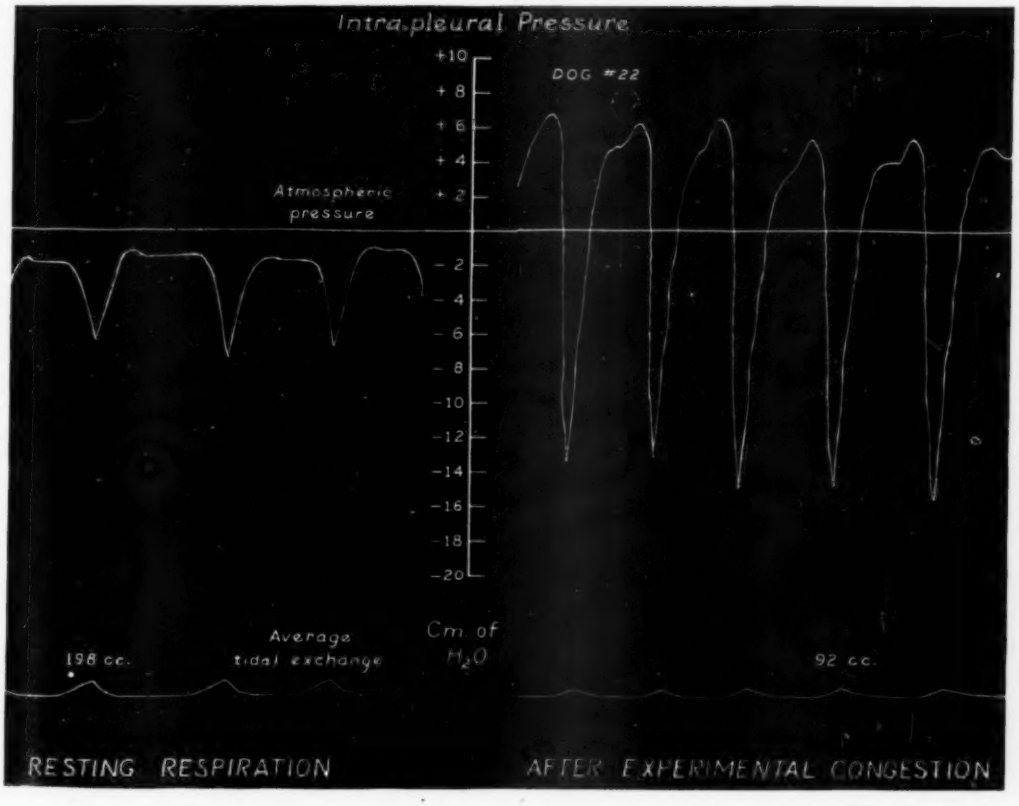

Fig. 1.—Effects of rapid intravenous infusion upon intrapleural pressure and tidal exchange (expressed per square meter of surface area).

TABLE II. INTRAPLEURAL PRESSURES (IN CM. H_2O)

DOG	QUIET BREATHING			AFTER CO_2 INHALATION			DURING MAXIMAL PULMONARY CONGESTION		
	INSP. AND EXP.	TOTAL	MEAN	INSP. AND EXP.	TOTAL	MEAN	INSP. AND EXP.	TOTAL	MEAN
20	−3.8 −7.8	4	−5.8	−7.8 −12.8	5	−10.3	+2.4 −8.8	11.2	−3.2
21	−3.6 −13.0	9.4	−8.3	−1.2 −15.0	13.8	−8.1	+5 −15	20	−5
22	−1 −5	4	−3	+ .4 −6.2	6.6	−2.9	+6.4 −14	20.4	−3.8
25	−1 −5.4	4.4	−3.2	−1 −5.8	4.8	−3.4	+2.6 −7.0	9.6	−2.2
26	−12* −14.6	2.6	−13.3	−11 −16.4	5.4	−13.7	+1.6 −3	4.6	− .7
27	−1 −8	7	−4.5	+8.4 −20.6	29	−6.1	+5 −17	22	−6
28	−3.4 −13.2	9.8	−8.3	− .6 −12.4	11.8	−6.5	+3.8 −5.8	9.6	−1
30	−2.2 −8	5.8	−5.1				+3.6 −8.2	11.8	−2.3
31	−2.4 −10	7.6	−6.2				+2.4 −7	9.4	−2.3
32	−2.6 −9.2	6.6	−5.9				+3.1 −8.2	11.3	−2.6
33	−2.6 −6.4	3.8	−4.5				+9.6 −12.4	22	−1.4
34	−2.8 −7.8	5	−5.3				+1.6 −6.2	7.8	−2.3
36	−4.6 −7.2	2.6	−5.9				+3.6 −5.8	9.4	−1.1
15	−1.0 −4.0	3	−2.5				+8.0 −1.0	9	+3.5
35	−2.2 −8.4	6.2	5.3				+ .4 −4.2	4.6	−1.9
Animals Vagotomized Before Congestion									
29	−2.1 −14.2	12.1	−8.05				+10.6 −22.4	33	−5.9
38	0	10.4	−5.2	+5.8 −17	22.8	−5.6	+9 −16.8	25.8	−3.9
39	−2.4 −11.2	8.8	−6.8				+2.4 −16	18.4	−6.8
A. B. V. 45	+ .5 −15.6	16.1	−7.55				+3.6 −17	20.6	−6.7
A. V. C.							+1.8 −12	13.8	−5.1

A. B. V. = After bilateral vagotomy.
A. V. C. = After vagotomy and cocainization of carotid bodies.
*The markedly negative pressures in this animal occured after instillation of iodized oil into the bronchi for visualization of the bronchial tree by x-ray.

the mean intrapleural pressure rose toward or above atmospheric levels. This was a constant phenomenon and confirms the work of Christie and Meakins,[1] who found similar results in patients with pulmonary congestion due to heart disease.

Alterations in Tidal Exchange and Ventilation.—The tidal exchange rose progressively during the administration of carbon dioxide, in some cases increasing by over 100 per cent (Table III). Similarly, ventilation was markedly augmented after the inhalation of carbon dioxide, occasionally increasing over threefold (Table IV). During increasing pulmonary congestion the tidal air, after a brief rise in many animals, decreased progressively (Table III and Fig. 1). The respiratory rate rose sharply in all animals during the early stages of congestion; during the terminal stages breathing became slow and labored. Corresponding to the changes in respiratory rate and the initial increase in tidal exchange, ventilation per minute rose during the early phases of infusion; later declining gradually, sometimes to values near or below the original resting levels (Table IV).

TABLE III. AVERAGE TIDAL EXCHANGE IN C.C. PER SQUARE METER

DOG NO.	RESTING	AFTER CO_2 INHALATION	DURING MAXIMUM PULMONARY CONGESTION
15	95	—	60
20	282	510	194
21	331	646	174
22	208	360	92
25	95	182	56
26	194	249	75
27	242	520	155
28	300	580	135
30	122	—	61
31	84	—	55
32	203	—	98
33	118	—	103
34	122	—	113
35	340	—	175
36	184	—	108
Animals Vagotomized Before Congestion and CO_2			
29	445	—	191
38	330	615	287
39	330	—	308
A. B. V. 45	141	—	367
A. V. C.	—	—	253

A. B. V. = After bilateral vagotomy.
A. V. C. = After vagotomy and cocainization of carotid bodies.

Changes in Respiratory Efficiency.—To determine the efficiency of respiration, the amount of tidal exchange (in cubic centimeters) produced per centimeter of change in intrapleural pressure was used as an index of efficiency:

$$\left(\frac{\text{Tidal exchange in cm.}^3 \text{ per square meter}}{\text{Total intrapleural pressure change per breath in cm. } H_2O}\right)^*.$$

By this method of determining respiratory efficiency it was found that during the administration of carbon dioxide the amount of tidal air breathed, for each centimeter of intrapleural pressure change, increased progressively from the resting state (Table V and Fig. 2).

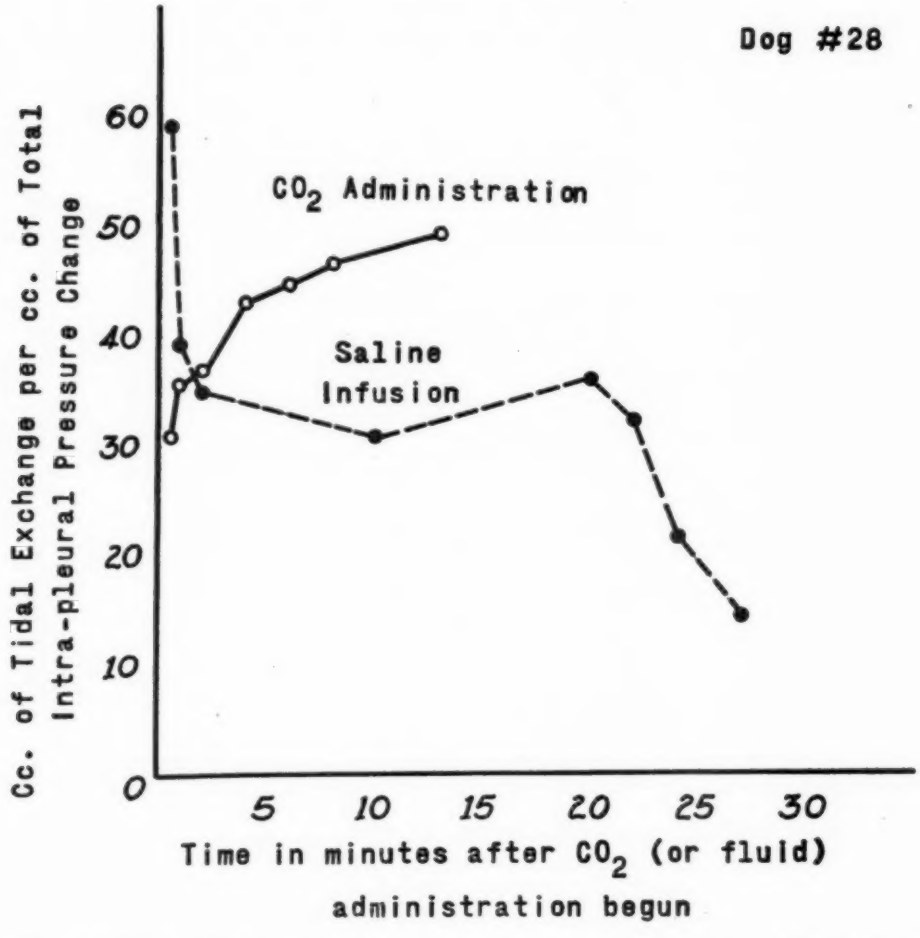

Fig. 2.—Graph showing alterations in tidal exchange produced for each centimeter of total change in intrapleural pressure. The tidal exchange per centimeter of intrapleural pressure change rises rapidly after carbon dioxide inhalation and falls progressively during intravenous infusion.

*This method of measurement of distensibility, or efficiency, involves the assumption that recoil from compression of the lungs during expiration is negligible. An alternate method of measuring intrapleural pressure changes is that of using only the negative pressure developed as an index of the force applied to the lungs. Since, in many cases, the portion of the pressure curve which was positive was very large, this latter assumption was obviously not feasible. It has been shown[1] that, although there is a slight amount of recoil after compression of the lungs, it is small in amount and we therefore have chosen to disregard it.

During pulmonary congestion caused by venous infusion, however, it will be seen (Table V, Fig. 2) that the amount of tidal exchange per centimeter of intrapleural pressure change decreased markedly at the height of pulmonary congestion. The response after carbon dioxide is evidence of increasing efficiency of respiration in the normal lung when an increasing stimulus is applied. On

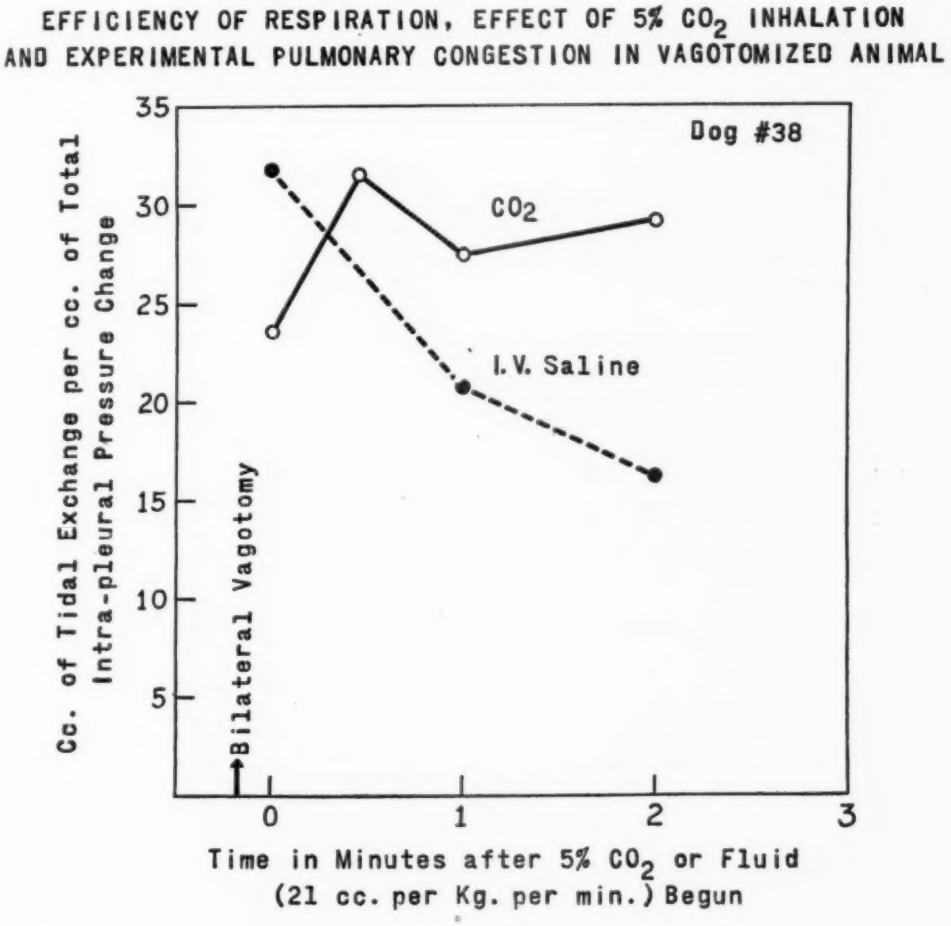

Fig. 3.—Vagotomized animal. Graph showing alterations in tidal exchange produced for each centimeter of total change in intrapleural pressure. The tidal exchange rises after carbon dioxide, and falls progressively during intravenous infusion. These findings are similar to those in the nonvagotomized animal (Fig. 2).

the other hand, although gross hyperpnea had supervened during pulmonary congestion, and although the intrapleural work expended had increased progressively, the efficiency of respiration and the amount of tidal exchange diminished rapidly during congestion.

TABLE IV. VENTILATION IN LITERS PER SQUARE METER PER MINUTE

DOG NO.	RESTING	AFTER CO_2 INHALATION	DURING MARKED PULMONARY CONGESTION
15	4.86	——	1.80
20	4.5	12.1	1.26
21	2.32	9.1	2.42
22	2.48	8.50	1.84
25	2.33	6.75	1.80
26	2.72	5.95	2.12
27	5.8	15.1	3.4
28	3.60	10.50	4.85
30	1.47	——	1.22
31	1.76	——	.88
32	3.05	——	1.66
33	1.41	——	1.54
34	3.50	——	2.70
36	1.47	——	2.76
35	4.09	——	3.50
	Following Bilateral Vagotomy		
29	3.11	——	0.38
38	2.64	6.76	1.75
39	2.64	——	3.77
A. B. V. 45	1.65	——	1.10
A. V. C.	——	——	1.01

A. B. V. = After bilateral vagotomy.
A. V. C. = After vagotomy and cocainization of carotid bodies.

TABLE V. RESPIRATORY EFFICIENCY $\frac{\text{CM.}^3 \text{ OF TIDAL EXCHANGE PER SQUARE METER}}{\text{TOTAL INTRAPLEURAL PRESSURE CHANGE (CM. } H_2O)}$

DOG NO.	RESTING	AFTER CO_2 INHALATION	DURING MAXIMUM PULMONARY CONGESTION
15	31.6	——	6.6
20	47.5	102	17.3
21	35.1	46.8	8.7
22	52.1	54.6	4.6
25	21.6	38.3	5.8
26	51.1	65.5	17.8
27	24.2	34.7	7.0
28	30.6	49.2	14.0
30	21.1	——	5.18
31	11.0	——	5.9
32	31.5	——	8.70
33	31.0	——	8.8
34	25.5	——	14.3
35	54.9	——	36.4
36	31.6	——	11.5
	Respiratory Efficiency Following Bilateral Vagotomy		
29	36.8	——	5.79
38	31.7	28.5	11.10
39	38.4	——	36.6
A. B. V. 45	25.7	——	17.8
A. V. C.	——	——	18.35

A. B. V. = After bilateral vagotomy.
A. V. C. = After vagotomy and cocainization of carotid bodies.

Chemical Alterations in the Blood.—Since the administration of large quantities of 0.9 per cent sodium chloride solution in a short period of time lowers the pH of the blood,[4-7] determinations of pH, arterial oxygen saturation, and serum carbon dioxide tension were made in these animals. In addition to 0.9 per cent sodium chloride solution, some animals were perfused with fluids containing a known amount of fixed base (solutions of 28 and 60 millimols of sodium bicarbonate per liter, rendered isotonic with sodium chloride) in an attempt to prevent the fall in pH of the blood, and the effects upon respiration were observed. Regardless of the chemical alterations in the blood (Table VI), the changes in mechanical efficiency of respiration were exactly parallel in the different animals, the efficiency of respiration diminishing progressively. Similarly, despite the different types of infusion, the tidal air decreased and the intrapleural pressure rose in all animals.

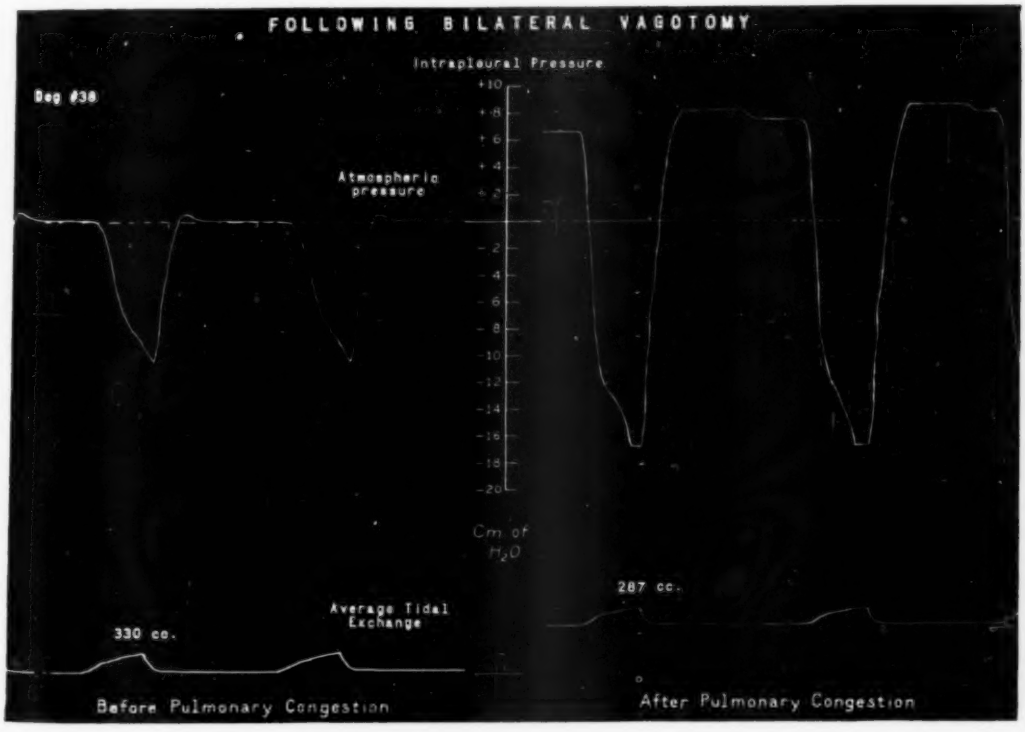

Fig. 4.—After vagotomy in the resting animal the respiratory rate slows, but expiratory pressure remains at atmospheric levels. After infusion of the vagotomized animal the total intrapleural pressure excursions increase markedly and the expiratory pressure rises well above atmospheric, while the tidal exchange (expressed per square meter of surface area) diminishes. The respiratory rate does not increase during infusion.

Effect of Vagotomy and Cocainization of Carotid Body and Sinus.—Vagotomy was performed on five animals which were then subjected to rapid venous infusions, producing pulmonary congestion. Vagotomy did not prevent either the

TABLE VI. CHEMICAL ALTERATIONS IN THE BLOOD

ANIMAL	INFUSING FLUID	BEFORE INFUSION			AFTER INFUSION			RESULTS
		pH	SERUM CO_2 TENSION (MM.-HG)	ARTERIAL SATURATION (PER CENT)	pH	SERUM CO_2 TENSION (MM.-HG)	ARTERIAL SATURATION (PER CENT)	CHANGES IN RESPIRATION
28 (Bilateral vagotomy)	0.9% solution of Sodium Chloride	7.56	22.7	90.1	7.05	48.5	90.5	Progressive decrease in respiratory efficiency and tidal air, rise in intrapleural pressure
29	0.9% solution of Sodium Chloride	7.65	20.2	88.5	7.46	17.06	90.1	
30	5 Gm. $NaHCO_3$ 5.55 Gm. NaCl/liter	7.3	51.4	92.1	7.3	69.7	91.8	
34	5 Gm. $NaHCO_3$ 5.55 Gm. NaCl/liter	7.3	36.6	90.1	7.3	85.4	90.8	
35	1.25 Gm. $NaHCO_3$ 7.30 Gm. NaCl	7.5	28.0	91.2	7.42	31	91.1	
45 Vagotomy and cocainization of carotid bodies	0.9% Sodium Chloride	7.30	——	——	6.80	——	——	

marked increase in intrapleural pressure fluctuations, with the shift of expiratory pressure readings above the atmospheric level, or the elevation of mean intrapleural pressures toward atmospheric levels (Table II, Fig. 4). The acceleration of the respiratory rate, which was seen in the intact animal, however, was not observed. Nevertheless, the efficiency of respiration (measured by the tidal exchange per centimeter of water of intrapleural pressure change) diminished progressively during infusion, after bilateral vagal section (Fig. 3).

Since the pH of the blood was found to fall markedly during the administration of 0.9 per cent sodium chloride, it seemed desirable to determine the extent to which peripheral chemoceptor mechanisms were stimulating respiration. Dog 45 was vagotomized and perfused rapidly with saline; Table II reveals that the total intrapleural pressure fluctuations increased markedly after infusion, while the expiratory and mean intrapleural pressures also rose. During the infusion, the pH of the blood fell markedly; from 7.30 to 6.80 (Table VI). Immediately after cocainization of the nerves to the carotid body and sinus, total intrapleural pressure fluctuations decreased markedly. Since the interruption of sensory impulses from the carotid sinus has been shown to stimulate respiration[8] this decrease in the motor activity of the respiratory muscles was considered as being caused by the blocking of impulses arising from stimulation of the carotid bodies, produced by the increase in hydrogen ion concentration. Thus, at least with the administration of large quantities of 0.9 per cent sodium chloride solution, peripheral chemoceptor mechanisms played a very important role in stimulating the respiratory center.

Effect of Section of the Cervical Cord.—Section of the spinal cord in the lower cervical region was performed at the height of congestion to abolish active expiratory movements. In each case an immediate sharp drop in tidal exchange occurred, sometimes to negligible levels (Table VII). Total intrapleural pressure

TABLE VII. EFFECT OF SECTION OF CERVICAL SPINAL CORD UPON RESPIRATION DURING PULMONARY CONGESTION

DOG NO.	TIDAL EXCHANGE (C.C.PER SQUARE METER)		INTRAPLEURAL PRESSURE CM. H_2O		TOTAL INTRAPLEURAL PRESSURE (FLUCTUATION CM. H_2O)	
	BEFORE CORD SECTION	AFTER CORD SECTION	BEFORE CORD SECTION	AFTER CORD SECTION	BEFORE CORD SECTION	AFTER CORD SECTION
30	61	27	+3.6 Exp. −8.2 Insp.	−1.4 Exp. −8.6 Insp.	11.8	7.2
31	55	No measurable exchange within 30 sec.	+2.4 Exp. −7.0 Insp.	+0.4 Exp. −1.8 Insp.	9.4	2.2
32	98	49.8	+3.1 Exp. −8.2 Insp.	−1.4 Exp. −6.1 Insp.	11.3	4.7
36	108	10	+3.6 Exp. −5.8 Insp.	+2.4 Exp. −4.2 Insp.	9.4	6.6

fluctuations diminished considerably; in some cases the expiratory intrapleural pressures diminished, but did not fall below atmospheric levels in all animals. If rapid venous infusion was continued in the animals in which abolition of expiratory movements caused a fall in expiratory intrapleural pressure levels, the mean and expiratory pressures again rose toward or above the atmospheric level (Fig. 5).

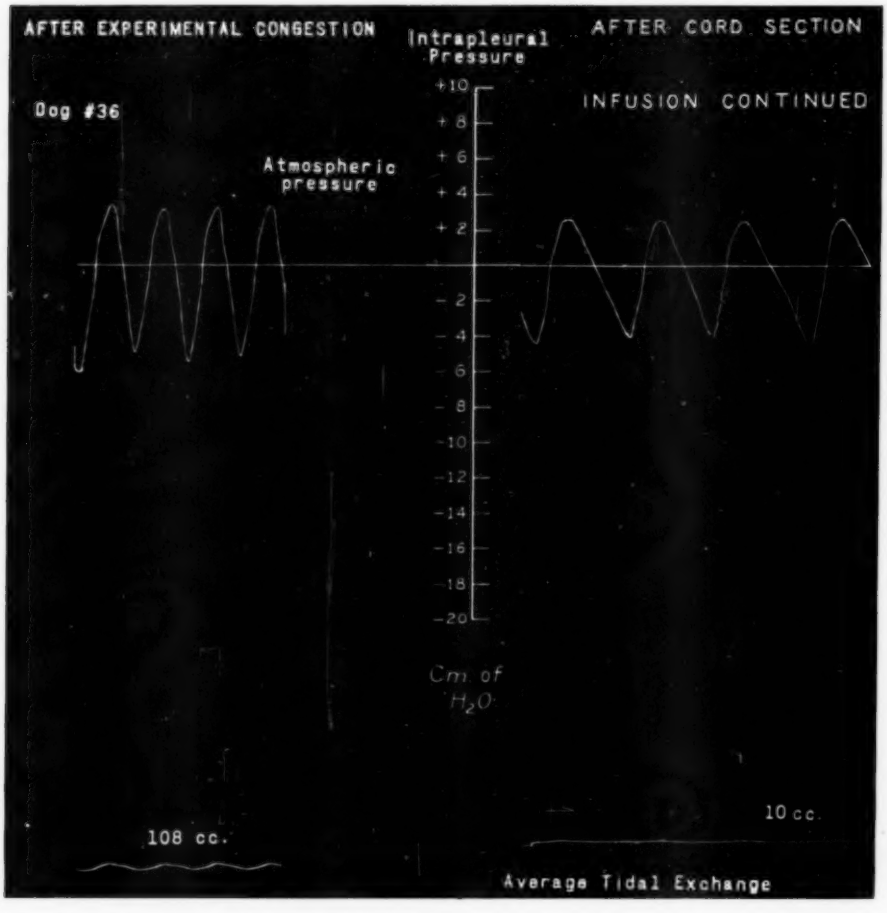

Fig. 5.—After section of the cervical cord (abolishing active expiratory movements) the expiratory intrapleural pressure remains above the atmospheric level if the intravenous infusion is continued, and the tidal exchange and ventilation fall to very low levels.

DISCUSSION

The importance of local changes in lung tissues in causing the labored and difficult respiration of pulmonary congestion seen in heart disease was pointed out in 1886 by von Basch,[10] who stated that while alveolar space and lung size increased after congestion of the lung, rigidity (Lungenstarrheit) of the pulmonary tissues also increased. Traube[11] contended, on the contrary, that en-

largement of the pulmonary vessels and their protrusion into alveolar spaces, with decrease in size of the latter, was the cause of the labored respiration. In 1927 Binger[12] proved that the lungs of patients with congestive failure contained an increased amount of residual air, which diminished in very severe congestion. In 1929 Churchill and Cope,[13] by producing experimental congestion of the lungs in animals, proved the role of nervous influences in causing a rapid and shallow type of respiration. Harrison[14] and co-workers further proved that the most important stimulus to rapid and shallow breathing seen in pulmonary congestion arose from vagal reflexes, not only in the pulmonary tissues but also from increased pressure in the great venous trunks of the heart and in the right auricle. Christie and Meakins,[1] in 1934, endeavored to correlate these observed phenomena by suggesting that the increased rigidity of the pulmonary tissues was caused by increased tension, and that the latter stimulated vagal endings, rendering the Hering-Breuer reflex hyperactive.

The present study indicates that as pulmonary congestion increases, the respiratory mechanism operates with progressively decreasing efficiency, expending a greater amount of work for a diminishing amount of tidal air per breath, and that these changes are independent of vagal reflexes. Christie and Meakins,[1] while demonstrating that elastic recoil of the lung was only moderately changed in pulmonary congestion due to heart disease, showed in patients that a greater fluctuation in intrapleural pressure was needed to achieve a given amount of tidal exchange, and stated that this was due to diminished "distensibility" of the lung.

It was further shown in the present study that, although the increase in respiratory rate after rapid infusion was prevented by bilateral vagotomy, the marked increase in intrapleural pressure changes and the diminished efficiency demonstrated after infusion were not prevented by section of the vagi. Since the extent of intrapleural pressure fluctuations was markedly diminished by cocainization of the nerves of the carotid body and sinus, it seems probable that a great portion of the reflex stimulation of respiration in the animals given 0.9 per cent sodium chloride was due to stimulation of peripheral chemoceptor organs by the fall of pH of the blood, caused by dilution of body base. Although the stimuli to breathing produced by rapid intravenous infusion were not further delineated in these studies, it is possible that they were multiple in nature. Among these possible sources should be considered (1) the effect of a lowered pH on the respiratory center itself,[15] (2) the effect of increased venous pressure in the cranial cavity,[16] and (3) stimulation of afferent fibers carried by the spinal cord from blood vessels in the limbs. In connection with the latter possibility, Moyer[9] has recently shown that distention of peripheral veins accelerates breathing in the nonvagotomized animal. The marked venous distention observed in the animals in the present study may have been a contributing factor in increasing the respiratory rate. Regardless of the origin of the afferent impulses stimulating respiration, the motor functions of respiration operated with decreased efficiency whenever pulmonary congestion was produced.

What are the factors responsible for this increased resistance to pulmonary filling and emptying? Von Neergaard and Wirz[17] have shown that the physical factors within the lungs which may alter their filling may reside in (a) the upper airway; (b) the lower airway and alveoli; and (c) the resistance of the pulmonary tissues themselves to deformation ("Deformationswiderstand"). Since in these experiments there was no alteration in the upper airway, it becomes evident that the causes of increased respiratory efficiency after carbon dioxide administration, and the decreased efficiency after experimental congestion, should be sought in changes in the smaller air passages and alveoli, and/or in the resistance of the pulmonary tissues to changes in shape and size. Since the physical properties of normal pulmonary tissues were apparently unaltered by carbon dioxide, it seems likely that enlargement of smaller bronchi and bronchioles occurred, resulting in a decreased frictional resistance to the entrace of air, and thus increasing respiratory efficiency. After congestion of the lungs, however, the efficiency of respiration fell progressively. Hence, alterations in either the size of smaller air passages and alveoli, and/or in the resistance of the tissues (to change of shape and size) must be assumed to have occurred with pulmonary congestion.

If the lungs and their vessels are considered as analagous to a type of erectile tissue, the resistance of the pulmonary tissues to changes in size and shape is readily understood. Von Basch's original demonstration that filling of the vessels of the excised lung caused an increase in lung size, with an actual increase in the air-containing space of the lung, indicated that as the vessels became distended and turgid they acted as an expanding, semirigid framework which increased the size of the enclosed air spaces. This finding was confirmed by Romanoff,[18] who also found that air entered the excised lung when the pulmonary vessels were filled with fluid. Weiss and Robb,[19] after extensive studies on patients with severe pulmonary congestion and cardiac asthma, concluded that the chest assumed a position of "functional emphysema" with the diaphragm fixed in an inspiratory position, and that an actual increase in total residual air occurred. Likewise, Binger[12] demonstrated an increase in residual air in patients with pulmonary congestion due to heart disease. The findings of the latter three authors can only be explained by the development of an increase in lung volume and air space caused by the erectile nature of the tissues of the congested lung.

When the changes in ventilation are considered in the light of the preceding findings, the cause of the increased effort exerted to achieve an adequate tidal exchange is easily understood. With increasing pressure in the lung vessels caused by the rapid infusions, the properties of resistance of the tissues to changes in shape and size became much enhanced. A much greater change in pressure had to be exerted upon the surface of the congested lung to produce expansion during inspiration. Similarly, during expiration the lung had to be actively compressed by an active contraction of the expiratory muscles to supplement the elastic recoil of the lung and to permit air to be expelled. As the turgidity of the pulmonary vessels increased, with mounting pulmonary congestion, the ventilation accomplished in relation to the work expended (measured by the

intrapleural pressure changes in inspiration and expiration) became progressively less. This concept is in exact accord with the observation of a marked decrease in the efficiency of respiration seen in these experiments with increasing pulmonary congestion.

The development of an enlarged semirigid lung imposes certain further mechanical disadvantages upon ventilation. A corollary to the demonstration of Weiss and Robb[19] that the congested lung becomes fixed in an inspiratory position is the development of a marked diminution of both complemental and supplemental air. Optimal tidal exchange then became possible only if total lung size were decreased by active compression of the lung by the expiratory muscles; reserve air had to be expelled by active effort from the air spaces before a maximal amount of air could enter the lung in the following inspiration. Proof of the vital role of the expiratory muscles in this regard was seen in the present study in the sharp diminution of tidal exchange which occurred immediately after the abolition of expiratory movements by section of the cervical cord.

The increased activity of expiratory muscles has certain other important connotations. In previous work one of us[20] has shown that pulmonary congestion caused by heart disease produced a labored type of respiration, with especial difficulty in expiration, and that the expiratory difficulty is much diminished by the administration of a bronchodilating drug (aminophylline). Although no direct observations of this type were made in the present study, our previous observations in patients suggest that a portion of the extra work expended to achieve ventilation in these animals, especially during expiration, was due to relative diminution in size of the smaller air passages. A further effect of the forced pulmonary compression by expiratory muscles is the facilitation of emptying of the congested pulmonary bed. Barach and Swenson[21] have shown clearly that an increase in intrapulmonary pressure during the expiratory phase exerts such an emptying effect upon the pulmonary circulation, and have made use of this principle in the treatment of pulmonary congestion and pulmonary edema.

Viewed in the light of the increased muscular activity demonstrated in the present studies in both inspiration and expiration during pulmonary congestion, the sensation of dyspnea in patients is more readily understood. In both phases of breathing the respiratory muscles are called upon to exert an unusual degree of effort, and also to operate at a definite mechanical disadvantage. Moreover, this increased activity must proceed over a relatively long period of time to insure the preservation of adequate ventilation. When the effort necessary to accomplish ventilation in the congested lung becomes very great, and when such exertion is prolonged, fatigue of the respiratory muscles occurs and the conscious recognition of this sensation of distress must inevitably follow. Moyer[9] has described the feeling of dyspnea as "a sense of specialized fatigue," an apt description of the series of events that occurs. Vagal reflexes control the rate and depth of respiration, terminating inspiration abruptly in the congested lung. This vagal control, however, would not seem to affect the relative disproportion between the work expended and the diminished tidal exchange achieved in pulmonary congestion. In this excessive effort necessary to ventilate the

congested lung, and in the fatigue resulting therefrom, would seem to lie the genesis of the complex sensation of dyspnea.

The shift in mean intrathoracic pressure toward atmospheric levels and above is not wholly due to increased activity of expiratory muscle groups, since abolition of their action did not cause the excursions above the atmospheric level to cease. Hence, although a portion of the upward shift may be due to these muscles, an increase in intrathoracic tension caused by overdistention of pulmonary vessels must also be an important factor. Traube's[11] contention that the congested capillaries encroach upon the alveoli, thus decreasing air space, is supported by the finding of a rapid fall in tidal exchange accompanied by a progressive rise in intrapleural pressure, in the terminal stages of pulmonary congestion in these animals. During extreme pulmonary congestion, even though intrapleural pressure fluctuations increased markedly, tidal exchange diminished precipitously, suggesting that alveolar air space was decreased in size by projection of the engorged pulmonary vessels into the alveolar lumen, or that the alveolar space itself remained unchanged but became filled with edema fluid. Binger[12] has also shown in patients that in advanced pulmonary congestion the residual air, which was at first increased, undergoes a diminution in volume. It seems probable, therefore, that diminution in alveolar space occurs but appears only in the later stages of severe pulmonary congestion.

CONCLUSIONS

1. A reconstruction of the dynamic changes in respiration from these studies indicates that the following events occur in pulmonary congestion:

(a) Accompanying the congestion, the pulmonary tissues undergo a marked increase in resistance to changes in shape and size. It is probable that relative obstruction also develops in the smaller air passages.

(b) Concomitant with the events in (a), increasing tension in the pulmonary tissues causes stimulation of vagal nerve endings, producing an acceleration of respiration and rendering the Hering-Breuer reflexes more sensitive.

(c) Tidal exchange is then accomplished in the congested and turgid lung at the expense of total greater changes in intrapleural pressure.

(d) As distention of pulmonary vessels and tissues with fluid increases, mean intrathoracic pressure rises toward atmospheric levels and expiratory intrapleural pressures rise well above the atmospheric level.

(e) Active participation of the expiratory muscle groups occurs when pulmonary congestion becomes marked. This increased activity is necessary to achieve optimal tidal exchange in the congested lung.

(f) These changes appear to be independent of alterations in carbon dioxide and hydrogen ion concentration of the blood.

2. In the intact animal the increase in respiratory rate with massive venous infusions is mainly of vagal origin, although the effect of increased pressure in the veins of the body and cranial cavity may play a contributory role in accelerating breathing.

3. Since rapid infusion of vagotomized animals produced marked increased in intrapleural pressure fluctuations, it is evident that the respiratory stimulation produced by such infusions arises not only from impulses mediated via the vagi, but also through other means.

The authors wish to express their gratitude to Dr. Tinsley R. Harrison for helpful suggestions and advice given throughout this study.

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PROLONGATION OF THE Q-T INTERVAL IN THE ELECTROCARDIOGRAM OCCURRING AS A TEMPORARY FUNCTIONAL DISTURBANCE IN HEALTHY PERSONS

With a Proposal That (Q-T) cal. May Be Used To Designate Q-T Intervals Calculated for the Physiologic Variables, Cycle Length, Age, and Sex

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VARIATIONS in the Q-T interval in the electrocardiogram may be due to several factors in addition to the heart rate. It is generally agreed that shortening of Q-T may result following the administration of digitalis[1] and that lengthening may be associated with hypocalcemia,[2] quinidine poisoning,[2] low blood potassium,[3] familial periodic paralysis,[3] beriberi,[4] diabetic coma,[5] cardiac enlargement,[5] and heart failure of various types.

In view of the increasing clinical significance now being ascribed to variations in the Q-T interval, it seems worthwhile to record the observation that Q-T may become temporarily prolonged in healthy persons as a result of the functional alterations associated with change in body position. This phenomenon was first observed in the course of examining an aviation cadet referred to us because of the complaint of postural dizziness.

The Q-T interval of the electrocardiogram became greatly prolonged, relative to the heart rate, when the aviator was tilted from the horizontal to a head-up position. Because of this Q-T finding, a further study was made.

Q-T TERMINOLOGY

Inasmuch as the duration of Q-T is affected by important physiologic variables, these relationships have been expressed by a number of empirical formulas. In these formulas, Q-T is allowed to vary with the square root,[6] cube root,[3] or logarithm[7] of the cycle length, and age and sex are taken into account by introducing a correction either in the formula itself or in the value derived from the solution of the formula. In this manner, Q-T is, in effect, calculated from certain physiologic variables and is sufficiently constant to provide a reference for the study of other variables which may affect Q-T duration.

This work was carried out at the School of Aviation Medicine and Research, Naval Air Station, Pensacola, Florida.

The opinions or assertions contained herein are the private ones of the writers, and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

Received for publication Feb. 15, 1947.

This calculated Q-T is variously designated. It is sometimes referred to as the systolic index, which expresses its relationship to the duration of systole; frequently it is referred to simply as Q-T, and the reader must determine whether the actual or calculated value is implied. We suggest, therefore, that the subscript "cal." (an abbreviation of calculated) be used to designate the Q-T interval which has been calculated from the physiologic variables according to one of the several proposed formulas. Thus, the general meaning of Q-T cal. would always be understood, and it would acquire more specific meaning if reference were made to the particular formula used in obtaining Q-T cal. values.

Q-T cal. is distinguished from the corrected Q-T (Q-Tc) of Taran and Szilagyi[8] as follows:

$$\text{Taran and Szilagyi's Q-Tc} = \frac{\text{actual Q-T}}{\sqrt{\text{cycle length}}}$$

$$\text{Q-T cal.} = K\sqrt{\text{cycle length}}$$

METHOD

Ten aviation cadets between the ages of 19 and 28 years served as subjects. All were healthy and without complaint except one (Case 1), who complained of loss of vision on suddenly standing erect, and of ease of blackout during certain flight maneuvers.

Each subject was allowed to lie on the tilt table for at least fifteen minutes, and a control electrocardiogram was taken at the end of this period. Lead II was then recorded (1) while the subject was tilted 60° head up, (2) during the first and fifth minutes after the tilt, and (3) while the subject was tilted back to the horizontal position. Careful measurements were made of the duration of Q-T and of cycle length, and the relationship between them was calculated using Bazett's formula,[6] $\text{Q-T} = 0.392\sqrt{\text{cycle length}}$, and Ashman's formula for adult men,[7] $\text{Q-T} = 0.375 \times \log 10\ (\text{cycle length} + 0.07)$.

RESULTS

A review of the several records obtained in each case showed that the maximum changes in Q-T cal. as compared with those in the actual Q-T occurred immediately after the subject was tilted. A summary of these maximal changes calculated both according to the formula of Bazett and that of Ashman is shown in Table I. It is seen that the changes are marked in one case, moderate in four, slight in four, and insignificant in one case. The electrocardiograms illustrating the greatest change (Case 1) are shown in Fig. 1. In the record taken immediately after the subject was tilted (Fig. 1,*B*) it is seen that the cycle length is greatly shortened, but that the duration of Q-T remains nearly the same. Thus, the change in the relationship of Q-T and cycle length is due to the failure of Q-T to shorten to a degree commensurate with the increase in heart rate. A

return toward the normal is seen in Fig. 1,*C*, taken nine minutes after the subject had been tilted. The same was true in varying degree for all other cases save one.

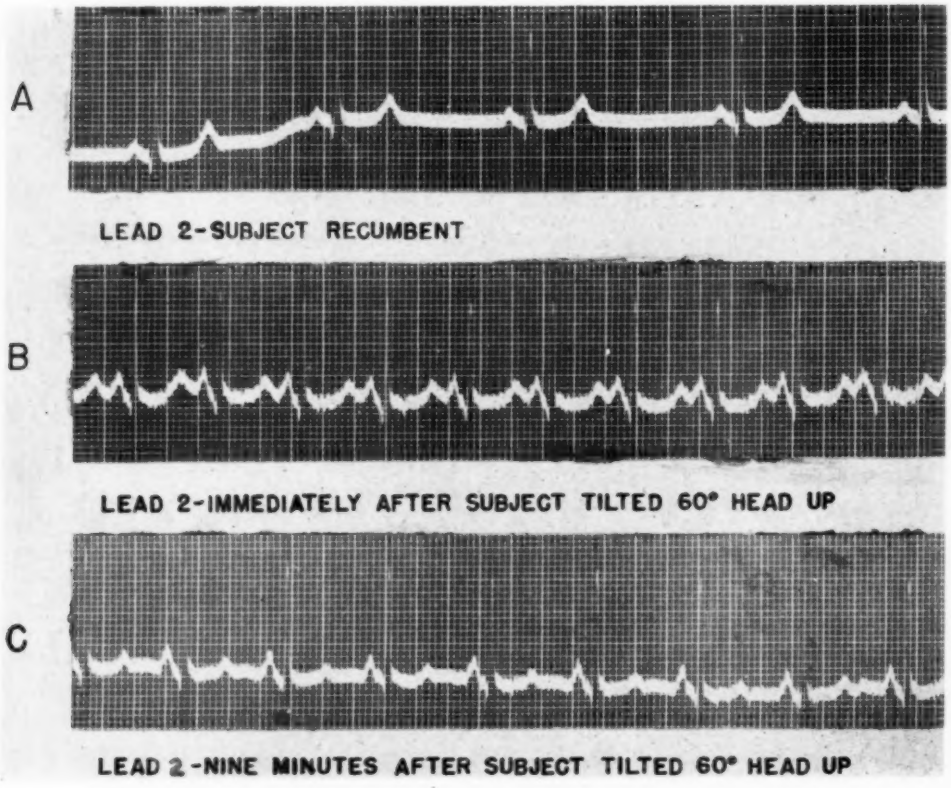

Fig. 1.—Case 1. Effects of postural change on electrocardiogram.

TABLE I. EFFECTS OF CHANGE OF POSTURE ON THE Q-T INTERVALS OF TEN HEALTHY YOUNG MEN

CASE NO.	CYCLE LENGTH		ACTUAL Q-T		Q-T cal.		Q-T cal		DECREASE ON TILT OF		ACTUAL Q-T
	FLAT	TILT	FLAT	TILT	FLAT BAZETT	TILT	FLAT ASH-MAN	TILT	BAZETT'S Q-T cal.	ASHMAN'S Q-T cal	
1	1.36	.57	.48	.46	.46	.30	.44	.31	.16	.13	.02
2	.98	.73	.40	.40	.39	.34	.39	.35	.05	.04	.00
3	.68	.60	.32	.32	.32	.30	.34	.32	.02	.02	.00
4	.95	.65	.35	.33	.38	.32	.39	.33	.06	.06	.02
5	.60	.51	.32	.29	.30	.28	.32	.29	.02	.03	.03
6	.87	.77	.37	.36	.37	.34	.38	.36	.03	.02	.01
7	.84	.84	.35	.36	.36	.36	.37	.37	.00	.00	−.01
8	.84	.68	.34	.32	.36	.32	.37	.34	.04	.03	.02
9	1.00	.81	.34	.34	.39	.35	.40	.36	.04	.04	.00
10	1.06	.62	.38	.30	.40	.31	.41	.32	.09	.09	.08

COMMENT

Since the Q-T interval represents the period of electrical ventricular systole (that is, from the time of the beginning of depolarization of the upper interventricular septum until the time of repolarization or the restitution of the polarized state in the ventricular septum and apical regions of the heart) we apparently are dealing, in these cases, with a retardation of the repolarizing process, such as might be produced by a decrease in the number of calcium ions in the blood. An explanation for the occurrence of this phenomenon in our cases is extremely difficult. It is reasonable to think that it might be due to sympathetic or parasympathetic influence, inasmuch as the relative change in Q-T occurs within a few seconds. Nevertheless, such a conclusion can only be verified by future electrocardiographic studies. Observations of the Q-T following the administration of such drugs as mecholyl, atropine, and epinephrine might provide a clue.

The influence of posture on the electrocardiogram has been studied previously,[9-12] in respect to various aspects of the cycle, including changes of the relative length of the Q-T interval. Bazett,[13] contrary to our findings, found that the Q-T segment was relatively decreased in length on *active* change of posture from the recumbent to the erect position. The formulas (mentioned heretofore) all assume that the Q-T will vary inversely with some function of the heart rate. This seems to be one instance in which the rate varies, but the Q-T remains practically the same.

SUMMARY

In the passive change of posture from the recumbent to the 60° head-up position, the relative value of the Q-T interval was very markedly increased in one case, moderately increased in four, and slightly increased in four; in one case, there was no significant change. This appears to be a transient, functional phenomenon, probably of neurogenic (sympathetic-parasympathetic) origin.

It is suggested that Q-T cal. can be used as a convenient designation to express the fact that the Q-T interval has been calculated for the physiologic variables: heart rate, age, and sex according to any one of the several formulas proposed for this purpose.

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Clinical Reports

DEATH FOLLOWING CORONARY THROMBOSIS IN A YOUNG WOMAN NINETEEN YEARS OF AGE

Case Report With Autopsy Findings

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A SEVERE degree of arteriosclerosis of the coronary arteries is rare in the first two decades of life. Zacks,[1] in his review of the pertinent literature, was able to find five cases of medial coronary sclerosis (and presumably infarction) in infants, and eight cases of coronary thrombosis in persons 10 to 20 years of age. To this latter group must be added Zacks' case and the case report by Jukl and Greenstein,[2] making ten in all. These cases were all men.

In so far as we are aware, the case presently to be reported is the first recorded instance of myocardial infarction in a woman under 20 years of age. White, Glendy, and Gustafson[3] have reported the case of a woman 22 years of age who survived acute myocardial infarction during pregnancy; coronary embolism was considered to be a remote possibility. The case of a still younger female has been reported by May.[4] His patient was 20 years of age and presented the clinical and electrocardiographic findings of acute infarction of the heart.

CASE REPORT

M. E. W., a young married woman 18 years and 11 months of age, entered the Naval Air Station Dispensary March 5, 1945, complaining of weakness. The family history disclosed nothing of medical significance. There was no past history of rheumatic fever, chorea, diphtheria, or tonsillitis. The patient stated that she had suffered from scarlet fever at 3 years of age but that there had been no complications. Thereafter, she remained well and healthy until three years before admission when there was a sudden onset of paralysis of the left lower portion of the face of unknown cause. Recovery from this disorder was complete in approximately one month. Urinalysis at that time showed albumin. The blood pressure was not taken.

Shortly after marriage (eight months prior to our examination), she experienced copious vaginal bleeding which ceased without treatment. Following this episode, there was progressive

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The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department, or the naval service at large.

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Received for publication Feb. 25, 1947.

loss of strength and appetite and she began to complain of severe headaches. However, it was not until three months before admission to the dispensary that she consulted a physician and was found to have high blood pressure. The treatment prescribed afforded some relief but did not abolish the symptoms.

Physical examination on admission revealed a frail, anxious person with moderate facial pallor. She was 5 feet, 4 inches in height and weighed 97 pounds. The temperature, pulse rate, and respirations were normal. The heart was found to be slightly enlarged. The sounds were of good quality except for accentuation of the aortic second sound. A slight systolic murmur was heard over the mitral area, but was not widely transmitted. The cardiac rhythm was regular at a rate of 86 per minute. The blood pressure was found to be 190/110. Examination of the ocular fundi showed the arteries to be contracted and irregular in size; there was arteriovenous nicking but no hemorrhages were seen. The peripheral arteries were soft. The remainder of the examination, including the neurological and psychologic aspects, revealed no definite abnormality.

The results of the laboratory studies were as follows: the erythrocyte count was 4.9 million per cubic millimeter; the hemoglobin was 102 per cent (Salhi); the leucocyte count was 7,850; and the differential was normal save for 6 per cent eosinophiles. Urinalysis showed 2 plus albumin, 6 to 8 white blood cells, and rare red blood cells per high power field. The erythrocyte sedimentation rate was normal, and the Kahn test was negative.

A diagnosis was made of essential hypertension and of hypertensive heart disease. The following additional studies were carried out, partly with the view of determining the patient's suitability for sympathectomy.

The basal metabolic rate was plus twenty. The electrocardiogram (Fig. 1), taken four days after entry shows complete A-V dissociation with an auricular rate of slightly over 100 and a ventricular rate of 50 per minute. In all other respects, the record is within normal limits save for rather low but upright T waves in Lead I and inverted (triphasic) T waves in Lead IVF. Teleroentgenogram of the chest revealed slight cardiac enlargement and slight prominence of the great vessels; the lung fields were clear. Intravenous pyelogram revealed no definite abnormality. Nine grains of sodium amytal were administered during the course of four hours with no significant reduction in blood pressure A Mosenthal renal function test was carried out and was considered to show borderline impairment of renal function.

Following the completion of the studies, the patient was advised to take a small amount of one of the barbiturates and was urged to enter a civilian clinic for further study.

Nothing more was heard from the patient until May 14, 1945, ten weeks after she was first seen. At noon, while walking slowly, she experienced moderate pain in the arms extending down to the fingertips, but there was no pain in the substernal or precordial areas. This was accompanied by a sensation of weakness, sweating, nervousness, and palpitation. Within three hours of the onset of these symptoms, she was seen by one of us (W. F. E.) at which time her symptoms had almost subsided. Examination revealed the temperature to be normal; the pulse rate, 78 per minute; and the blood pressure, 196/120. No cyanosis was observed. The rhythm of the heart was regular and the heart sounds were of good quality. No murmur or friction rub was heard. The lungs were clear.

She was advised to rest quietly at home. That evening she awakened from a nap much refreshed and when asked by her landlady how she felt, answered: "I feel fine and I think I'll eat some of that fried chicken you are cooking." With this the landlady walked out of the room, but hurried back when she heard a "gurgling" sound, and found that the patient had died.

Autopsy.—Permission was granted for an autopsy limited to the heart, kidneys, and adrenals.

The aorta was smooth and elastic along its entire length except for numerous elevated atheromatous lesions, including plaques in the region of the coronary ostia.

The heart, the proximal 15 cm. of the aorta, and a small attached portion of the pulmonary artery, trachea, and tracheal nodes weighed altogether 395 grams. The wall of the right ventricle measured approximately 5 mm. in thickness, and the wall of the left ventricle, 2 centimeters.

In the endocardium of the right ventricle, 5 mm. below the attachment of the posterior commissure of the tricuspid valve, there was a smooth white area of superficial thickening. Five

millimeters below this there was an area of fibrosis about 2 mm. in diameter. The posterior papillary muscle showed a well-defined area approximately 1 x 0.5 cm. which was white and smooth, and which on sectioning appeared to be endocardial thickening or superficial fibrosis. The valves showed no lesions.

Multiple cross sections through both coronary arteries revealed marked thickening of the walls and narrowing of the lumen. The right coronary orifice was narrowed. The right coronary artery appeared to be completely occluded by a thrombus approximately 4 cm. from its origin. The lumen of the left coronary artery, 1.0 cm. from its origin and just proximal to the origin of its circumflex branch, was reduced to a narrow slit by atherosclerosis.

Sections of the posterior wall of the right ventricle, taken through the areas described, showed hypertrophied muscle fibers interspersed with extensive connective tissue hyperplasia and replacement fibrosis, the continuity of muscle fibers being lost by intervening fibrous tissue.

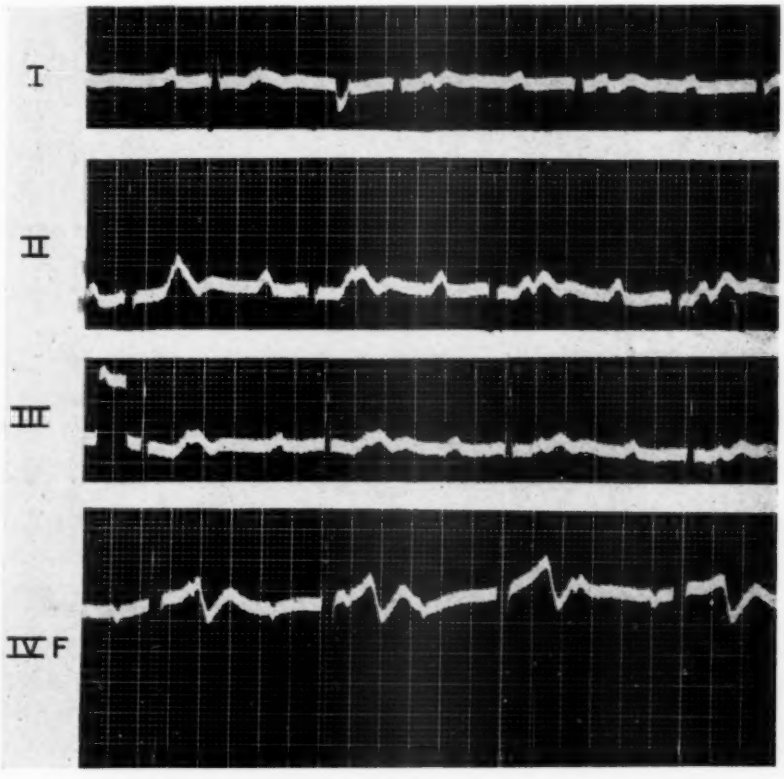

Fig. 1. —Electrocardiogram taken ten weeks before death, showing complete A-V dissociation in the case of a woman 19 years of age, who died following coronary thrombosis.

In a section of the anterior wall of the right ventricle the changes were most striking in the epicardial tissue, which showed proliferation of the endothelial surface of the visceral pericardium, edema, and infiltration by diffusely scattered lymphocytes.

The anterior wall of the left ventricle, in a section taken through the base of the septum, showed fibrosis similar to that described in the contiguous portion of the right ventricular wall. The most extensive area of fibrosis was just beneath the endocardial surface which was involved in focal lymphocytic infiltration, beneath which there was an area of hyaline necrosis.

Fig. 2.—Microphotograph of section of right coronary artery, showing clot still partly adherent to lumen

Fig. 3.—Microphotograph of section of left coronary artery, showing marked atherosclerotic changes of the intima.

Sections of the right coronary artery taken from 4 to 5 cm. from its origin (Fig. 2) showed that the lumen was eccentrically narrowed by irregular elevations of the endothelium, which had a frayed appearance showing loss of cell structure, and foci of necrosis beneath which there were deposits of lipoid and fatty globules. There was marked cellular infiltration of the media and subintima by lymphocytes, plasma cells, and a smaller number of polymorphonuclear leucocytes. A fresh thrombus occluded the small, distorted lumen.

A section of the left coronary artery, 1 cm. from its origin (Fig. 3), showed thickening of the vessel wall with distortion and narrowing of the lumen. The endothelial surface was interrupted by irregular elevations characterized by subendothelial collections of lymphocytes and surface deposition of fibrin and clumps of erythrocytes. Beneath these areas, cholesterin crystals, hyaline degeneration, and two foci of necrosis were seen.

The wall of the ascending aorta, in a section taken just below the arch, showed proliferative and degenerative changes in the intima characterized by hyaline necrosis and cholesterin deposits. In the adventitia, the perivascular tissue around the vasa vasorum showed collections of large mononuclear cells, unusually large plasma cells, and small areas of hyaline or fibrillary appearance.

In the kidney, several small foci of lymphocytic infiltration were found in the cortex, located just beneath the capsule, and associated with fibrosis or hyalinization of the glomeruli in immediate proximity. There was no diffuse fibrosis or degenerative change, the glomeruli of other portions showing normal histologic structure. The small vessels seen in the section showed no lesions.

A section of the adrenal showed the normal histologic structure.

SUMMARY

The history and autopsy findings have been presented in the case of a 19-year-old woman with hypertensive and coronary heart disease, who died following coronary thrombosis. The striking feature of the case is the age at the time of death. This is the first recorded instance, as far as we know, of a woman under the age of 20 years with this disorder.

There was no evidence of rheumatic fever, diabetes, or xanthomatosis, factors which may be responsible for the precocious development of arteriosclerosis or atherosclerosis. However, the arterial hypertension almost surely was an important etiologic factor in this regard. The cause of the hypertension was not determined. It was not secondary to coarctation of the aorta, polycystic kidney disease, nephritis, aberrant renal artery, or tumor of the adrenal gland.

Complete A-V heart block was present at the time one of the examinations was carried out. It can be readily explained on the basis of impaired blood supply to the specialized conduction tissue. The fact that it was present only as a temporary phenomenon suggests that rather dramatic changes in blood supply to the conduction tissue occurred during the period prior to the terminal events.

We are indebted to Lieutenant Commander Eleanor W. Townsend, Medical Corps, United States Naval Reserve, pathologist, U. S. Naval Hospital, Pensacola, Fla., for the pathologic findings in this case, and to Dr. William B. Porter of the Medical College of Virginia for taking the microphotographs.

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PERICARDIAL EFFUSION DUE TO HEMOLYTIC STREPTOCOCCUS FOLLOWING AN ACUTE UPPER RESPIRATORY INFECTION; ASSOCIATED PLEURAL EFFUSIONS

Report of Case and Review of Literature

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THERE have been an increasing number of reports[1-8] of the association of acute pericarditis, with or without effusion, with an acute upper respiratory infection. However, the isolation of the hemolytic streptococcus from the pericardial effusion in this syndrome is unusual and prompted this report.

CASE REPORT

W. J., a 52-year-old white taxicab driver, became ill in the first week of August, 1946, with the onset of a sore throat accompanied by chills and a feverish feeling. For the following three weeks the patient medicated himself with aspirin, saline gargles, and topical argyrol. Because of continuation of the sore throat and fever, he consulted a physician on Aug. 22, 1946, who found an exudative, bilateral, follicular tonsillitis with bilaterally tender and enlarged anterior cervical glands. Because of distant heart sounds, an x-ray film was made. This revealed an enlarged cardiac shadow, which was interpreted as being due to a pericardial effusion (Fig. 1).

The patient was put on oral penicillin, 100,000 units every four hours, which he continued to take until his admission to the hospital six days later; this was necessitated by the onset of increasing orthopnea and pain in the anterior part of the chest, both of which were relieved by assuming the upright position. He entered the hospital on Aug. 28, 1946. Further questioning on admission did not reveal a previous history of rheumatic fever, heart disease, malaria, or any of the enteric fevers. The patient stated that a week prior to the onset of his illness all of his family, including himself, drank some raw milk, but that he was the only one who became ill.

The physical examination revealed the patient to be well developed and nourished. He was dyspneic, orthopneic, and slightly cyanotic. The rectal temperature was 100° Fahrenheit. The pharynx was normal. There were no distended neck veins in the erect position. There was dullness on percussion and diminished breath and voice sounds on auscultation over the left lower lobe posteriorly. The heart was thought to be enlarged slightly to the left. The sounds were distant. No murmurs were heard. The radial pulse and ventricular rates were 80 per minute and regular. The blood pressure was 100/76. The spleen was felt 3.0 cm. below the costal margin on inspiration and was firm. The liver was not felt. No peripheral edema was present.

There were 7,600 white blood cells per c.mm., with 81 per cent neutrophiles. The urine analysis showed a specific gravity of 1.020, the reaction was alkaline, there was no sugar nor albumin, and the microscopic examination was normal. The blood sedimentation rate was 50 mm. at the end of one hour. Roentgen examination of the chest on admission (Fig. 2) showed a moderate degree of pleural effusion at the left base and a slight enlargement of the cardiac sil-

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Received for publication Feb. 10, 1947.

houette. The blood nonprotein nitrogen was 32 mg. per cent. The serum total protein was 7.46 Gm. per cent, with 4.33 Gm. of albumin, 3.13 Gm. of globulin, and an albumin-globulin ratio of 1.38. The venous pressure in the right antecubital vein was 120 mm. of water. The circulation times revealed an arm-to-tongue (calcium gluconate) time of 14 seconds and an arm-to-lung (ether) time of 6 seconds. Agglutination tests for typhoid, paratyphoid, typhus, and brucellosis were negative. The brucella skin test was negative after forty-eight hours. A blood culture was negative. An electrocardiogram (Fig. 3,*A*) showed the T waves to be inverted in Leads I and IV and diphasic in Lead II. The electrocardiogram was interpreted as being consistent with the diagnosis of pericarditis in the subacute or chronic stage.

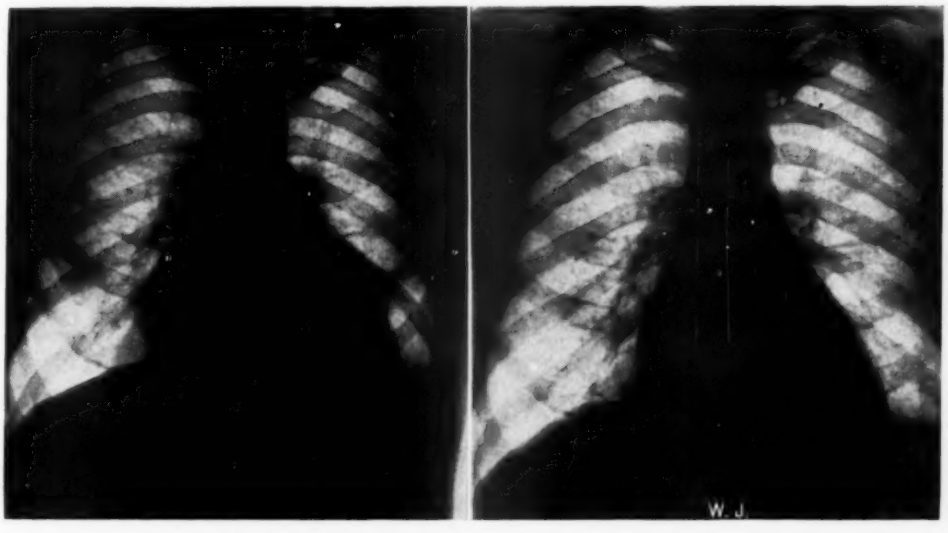

Fig. 1.—Aug. 22, 1946 (six days before hospitalization). *X*-ray of chest shows enlarged cardiac silhouette due to pericardial effusion and obliteration of left costophrenic space.

Fig. 2.—Aug. 30, 1946 (third day of hospitalization). Note that the cardiac shadow has decreased considerably, but that the left pleural effusion persists.

The course in the hospital is shown in Fig. 4. During the first few days in the hospital, the dyspnea and orthopnea, so prominent on admission, practically disappeared only to recur on September 3, seven days after hospitalization. This was associated with a shaking chill and a temperature of 100.6° Fahrenheit. A blood culture was negative. Thoracentesis of the left pleural cavity was done on September 5, and 4.0 c.c. of a thick, light yellow, gelatinous fluid were evacuated. Both the culture and the smear of this fluid for acid-fast organisms were negative. On September 10, with the temperature at 102.8° F., the patient was started on intramuscular penicillin, 30,000 units every three hours day and night.

On September 12, a pericardial tap in the left fifth intercostal space anteriorly at the nipple line was performed and about 65 c.c. of a light yellow, thick, fibrinous fluid was obtained. The fluid had a specific gravity of 1.020 and contained many red and white blood cells. Of the white blood cells, 75 per cent were polymorphonuclear leucocytes and 25 per cent were lymphocytes. The protein content was 3.53 Gm. per cent. Culture yielded a pure growth of *Streptococcus haemolyticus*. Smear for acid-fast organisms was negative. A cell block showed a sediment made up of fibrin, red blood cells, leucocytes, and many large slightly eosinophilic cells containing one or more nuclei which tended to be rather large. Many of the neclei had prominent nucleoli. No tumor cells were seen. Guinea pig inoculation was negative. The blood sedimentation rate at this time was 110 mm. at the end of one hour.

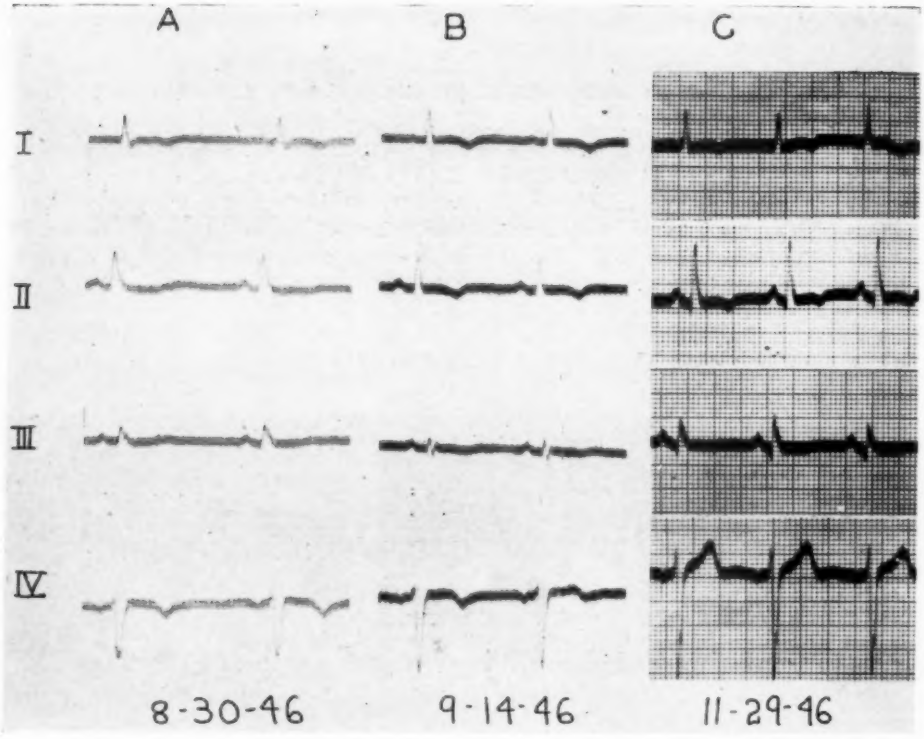

Fig. 3.—*A*, Electrocardiogram taken on third hospital day. T_1 and T_4 are inverted; T_2 is diphasic. *B*, Eighteenth hospital day; T_1 and T_2 are further inverted. *C*, Approximately one month after leaving hospital; T_1 and T_2 are still inverted, T_4 is now upright.

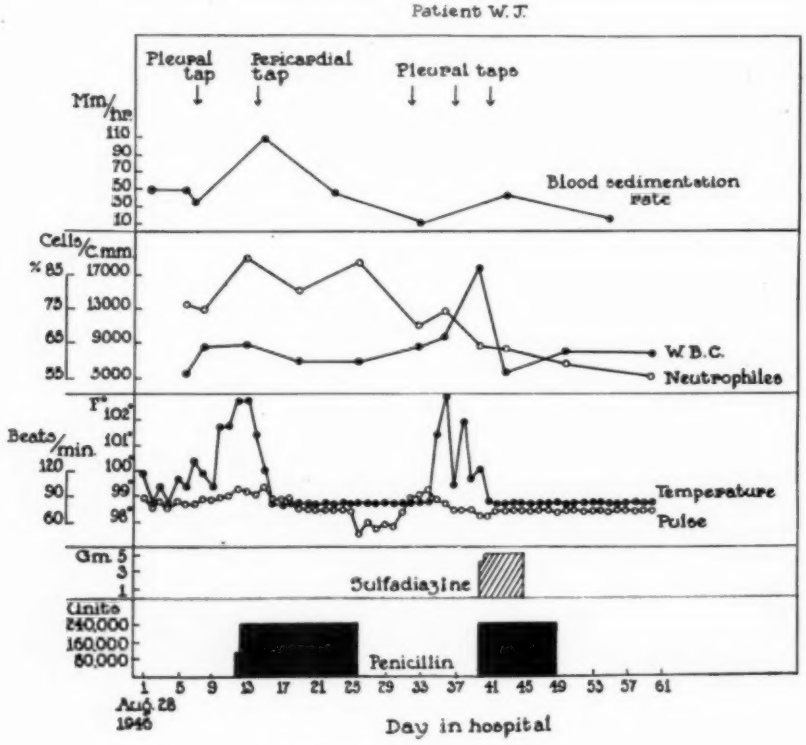

Fig. 4.—Chart of course in hospital.

Following this paracentesis, there was marked relief of the dyspnea and orthopnea. Six days later, this procedure was repeated with the purpose in mind of injecting air into the pericardial sac for roentgen confirmation of a pericardial effusion. However, despite needling at the same site as previously, no fluid was obtained. The penicillin was stopped on September 23 after a total of 3,060,000 units had been given in thirteen days. While the serial x-ray films (Figs. 5, 6, and 7) showed a decrease in the size of the cardiac silhouette, they also revealed a progressive increase in pleural fluid at the left base. Thoracenteses were done in the left eighth intercostal space posteriorly on September 28, October 3, and October 7. At the first thoracentesis, 220 c.c. of a straw-colored fluid with a specific gravity of 1.020 and a total protein of 3.35 Gm. per cent were obtained. The fluid was cultured and a smear examined for acid-fast organisms. Both were negative. The second chest tap produced 900 c.c. of a bloody fluid with a total protein of 3.06 Gm. per cent, which was negative on culture and for acid-fast organisms. A cell block revealed no tumor cells. An inoculated guinea pig showed no evidence of tuberculosis. The third tap was productive of 600 c.c. of bloody fluid with a total protein of 3.41 Gm. per cent. Culture of the fluid and smear for acid-fast organisms was negative.

An electrocardiogram taken on September 14 (Fig. 3,*B*) showed further inversion of T_1 as well as of T_2, as compared with the admission graph (Fig. 3,*A*).

On October 2, there was another rise in temperature to 102.6° F., accompanied by a recurrence of the dyspnea and orthopnea. A pleuropericardial friction rub was heard in the left fifth intercostal space anteriorly at the level of the nipple. The white blood count rose to 17,700 cells per c. mm., with 63 per cent neutrophiles. The blood sedimentation rate was 40 mm. at the end of one hour. Intramuscular penicillin, 30,000 units every three hours day and night, and oral sulfadiazine, 5.0 Gm. daily, were started on Oct. 7, 1946. The temperature was normal by the next day. Sulfadiazine was discontinued after 29 Gm. had been given because of the appearance of crystals in the urine. The penicillin was stopped on October 16 after 2,400,000 units had been given in ten days.

By October 24, the patient had improved sufficiently to be discharged. The spleen was still palpable and there was minimal effusion at the base of the left lung. The blood sedimentation rate was 17 mm. at the end of one hour. The white blood count was 7,500 cells per c.mm. with 55 per cent neurophiles.

The patient was re-examined on November 29. He had no complaints. The lungs were clear to percussion and auscultation. The heart was not enlarged and the sounds were good. The radial pulse and ventricular rate were 80 per minute. The spleen was felt about 0.5 cm. below the costal margin on deep inspiration. There was no enlargement of the liver and no peripheral edema. An x-ray of the chest (Fig. 8) showed the heart to be normal in size and the lungs to be clear. The electrocardiogram (Fig. 3,*C*) still showed inversion of T_1 and T_2, but T_4 had become upright.

COMMENT

Although reports on the association of an upper respiratory infection with an acute pericarditis (with or without concomitant effusion) are becoming more numerous, the isolation of a definite etiological agent in these cases is still unusual. Gardner[1] obtained complete recovery by treating with Prontylin one patient with a hemolytic streptococcus pericarditis which followed a pharyngitis and tonsillitis. This was the only reported instance in which this organism was cultured from the pericardial fluid. Willius[3] and Levine[4] infer that the streptococcus found in the throat may have been the causative agent for the pericarditis in their cases, but describe neither taps nor cultures to substantiate this point.

Nathan and Dathe[7] report eight cases as instances of respiratory infection and pericarditis. Five patients had an associated pericardial effusion and, on paracentesis, four of these were found to be hemorrhagic. Culture, smear, and guinea pig inoculation of the fluid yielded no organisms. In one patient there

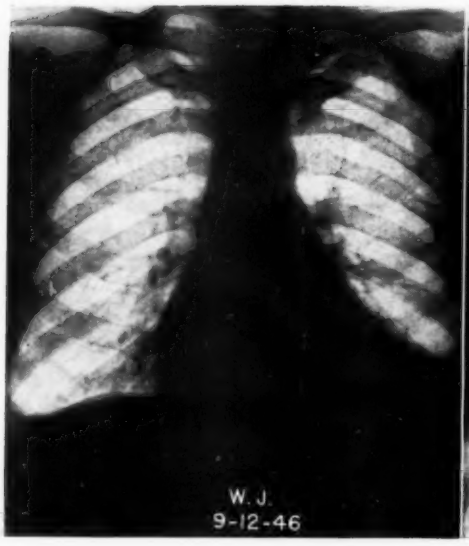

Fig. 5.

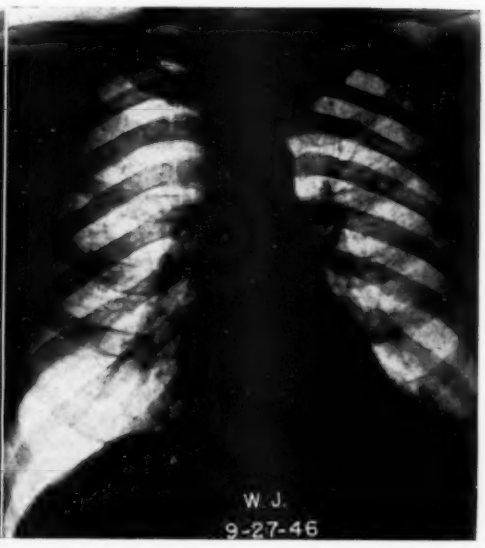

Fig. 6.

Fig. 5.—Sixteenth day of hospitalization. Note bilateral pleural effusions.
Fig. 6.—Thirty-first hospital day. Cardiac shadow is normal in size. Fluid at left base still present.

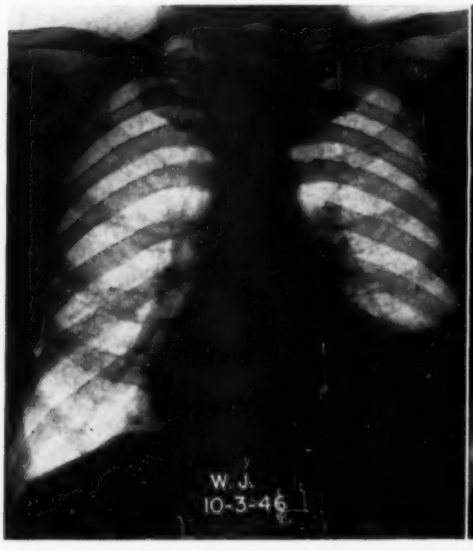

Fig. 7.

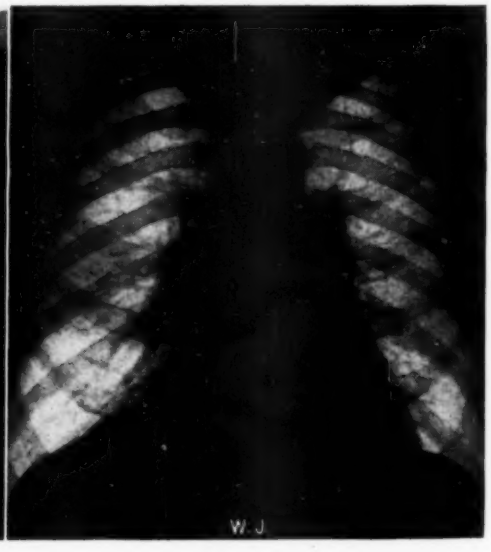

Fig. 8.

Fig. 7.—Thirty-seventh hospital day. Note marked increase in left pleural effusion. Thoracentesis evacuated 900 c.c. of hemorrhagic fluid.
Fig. 8.—Approximately one month after discharge from hospital. X-ray of heart and lungs is normal.

was an associated pleural effusion. The peripheral white blood count varied between 6,000 and 27,400 cells per cubic millimeter. They postulate that involvement of the pericardium may occur by spread from the contiguous hilar lymph nodes or by a hypersensitive response of the pericardium to an offending organism, the immune reaction of the body being inadequate.

Nay and Boyer[5] review fifteen cases of acute pericarditis in which the etiology was undetermined. The existence of an associated upper respiratory infection is not definitely stated. None of these patients had any past or present history of rheumatic fever. In ten patients, there was a pericardial effusion. In twelve instances, the onset of the pericarditis was extremely abrupt, with sudden severe precordial pain and usually with chills and fever. The pain was aggravated by deep respiration, and by twisting the trunk and by swallowing. Leucocytosis was exceptional; only four patients had white counts above 9,000 cells per cubic millimeter. These counts were 12,000, 21,000, 16,000, and 33,000 cells, respectively. Fourteen patients had electrocardiographic evidence suggestive of pericarditis.

Smalley and Ruddock[8] report three cases of pericarditis following pharyngitis. One case is reported in detail. Three pericardial paracenteses yielded a total of 1,870 c.c. of a cloudy yellow fluid but in none was a positive culture obtained. The patient was treated successfully with 3,840,000 Oxford units of penicillin parenterally.

Hall[9] in 1925 cured a patient with intravenous mercurochrome after a hemolytic streptococcus (isolated from the blood stream) had resulted in an acute pericarditis. There was no concomitant effusion, so that no culture was taken directly from the pericardial sac.

The course of events in our patient's illness would then seem to be as follows: his illness started with tonsillitis. Although we have no cultural proof, we strongly suspect that the tonsillitis was the result of streptococcic infection since Rantz, Boisvert, and Spink[10] have shown that the combination of exudative tonsillitis and pharyngitis with tender anterior cervical glands permits the diagnosis of a hemolytic streptococcus infection with a high degree of accuracy, even without a bacteriologic study of the flora of the throat. Within three weeks, a pericarditis with effusion had occurred which necessitated hospitalization. Culture of the pericardial fluid on one occasion yielded a pure growth of hemolytic streptococcus. The course was complicated by left pleural effusion which was repeatedly sterile. Two courses of parenteral penicillin were necessary to combat the infection. The success with penicillin is not unexpected.[11]

The electrocardiographic picture (Fig. 3) is compatible with pericardial involvement in the later stages.[12] Young[6] and Rantz, Spink, and Boisvert[13] have shown, however, that similar electrocardiographic findings may occur with upper respiratory infections in the absence of clinical pericardial involvement.

SUMMARY

1. A case is presented of a 52-year-old man with pericardial and pleural effusion which followed an acute upper respiratory infection. Culture of the

pericardial fluid yielded a hemolytic streptococcus. Treatment with penicillin was successful.

2. The literature is reviewed, and the rarity of isolation of the hemolytic streptococcus from the pericardial effusion in such cases is stressed.

ADDENDUM

The patient was last seen on Oct. 22, 1947, a year after discharge from the hospital. The heart was normal in size. Blood pressure was 150/90. The spleen was no longer palpable. The electrocardiogram showed T_1 and T_2 to be upright, though low.

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INTERATRIAL SEPTAL DEFECT ASSOCIATED WITH SYPHILITIC AORTIC INSUFFICIENCY

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A RECENT post-mortem study has clarified an apparent clinical inconsistency and has revealed to us a combination of cardiac lesions which may be diagnosed prior to death. Syphilitic aortic insufficiency, coexisting with a large interatrial septal defect, was demonstrated in one case. The files of over 30,000 autopsies performed from 1929 to 1946 at the Los Angeles County Hospital contained only one other case of a similar nature.

The physical signs, when associated with the electrocardiograms and roentgenograms, are fairly distinctive.

There are several excellent articles which are quite complete reviews of the literature in regard to interatrial septal defect and associated acquired valvular lesions. McGinn and White[1] in 1933 presented and summarized the clinical and pathologic findings in twenty-four cases showing the combination of mitral stenosis and interatrial septal defect. Roesler[2] in 1934 reviewed sixty-two cases illustrating the clinical and anatomic peculiarities of interatrial septal defects. In at least three-fourths of these cases, valvular lesions were found which affected predominately the mitral orifice. There was no case with an isolated definite aortic regurgitation associated with the septal defect present in his series. Tinney[3] in 1940 reported two autopsied cases of uncomplicated interatrial septal defect. He also reported on twenty-two others gleaned from the literature since Roesler's review. He found that 68 per cent of the twenty-two cases had chronic valvular lesions. In one-half of these the lesion was mitral stenosis. Burrett and White[4] in 1945 presented a clinical analysis of comparative studies in the sixty-two cases collected by Roesler and thirty-one autopsied cases collected since that date. Certain criteria for the recognition of uncomplicated interatrial septal defect, as well as for the recognition of the septal defect associated with mitral stenosis, were presented. Mitral stenosis was found in nineteen of the thirty-one cases.

The association of syphilitic aortitis, mitral stenosis, and interatrial septal defect was reported by Kirshbaum and Perlman[5] in 1939. As the patient died on admission to the hospital, there was no time for a clinical study of this case. With this exception, the literature contains no report which the author could find associating interatrial septal defect with aortic insufficiency on a syphilitic basis.

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Received for publication March 5, 1947.

In keeping with the established criteria as presented by several of the authors here noted, the files of the Los Angeles County Hospital were searched for cases of interatrial septal defect. Twenty-three cases were found in which the defect was greater than 1.0 cm. in diameter and in which no other congenital cardiac anomaly was present. All patients in this series were older than one year of age. Of these, nine had an associated mitral valvulitis. Only two patients had aortic incompetence due to syphilitic aortitis. The latter two cases form the substance of this report.

CASE REPORTS

CASE 1.—F. M., a 60-year-old Mexican farmer, first entered the Los Angeles County Hospital on Feb. 16, 1945, because of pain in the precordium which was aggravated by eating a heavy meal and by exercise. He also had ankle edema during the day. These symptoms had been present

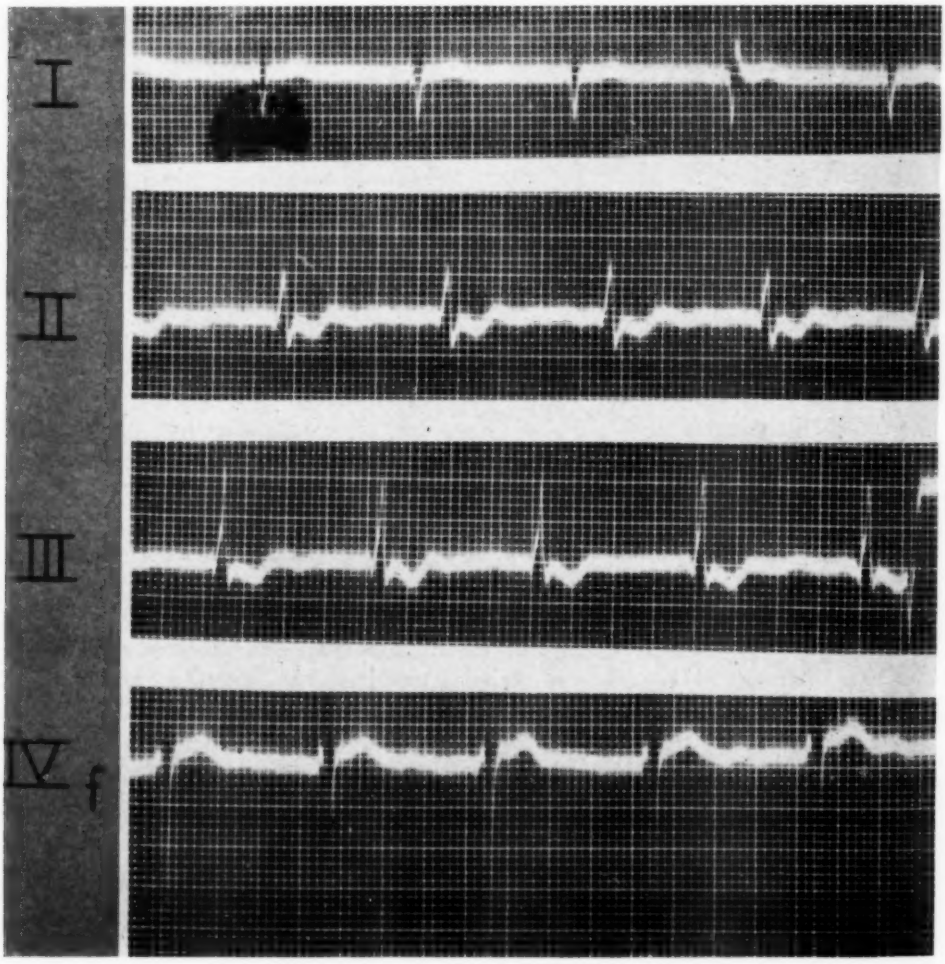

Fig. 1.—Case 1. The electrocardiogram shows right axis deviation, auricular fibrillation, and digitalis effects.

for only a few weeks. A summary of the past history revealed that his blood Wassermann was positive in 1937 and 1938. He received a course of twenty-four intravenous and twelve intramuscular injections. The patient was discharged on March 9, 1945, on a cardiac regimen. He was followed both in the hospital and in the outpatient clinic until his death on Sept. 15, 1946. His last admission to the hospital was on Sept. 10, 1946, when he entered in severe congestive heart failure.

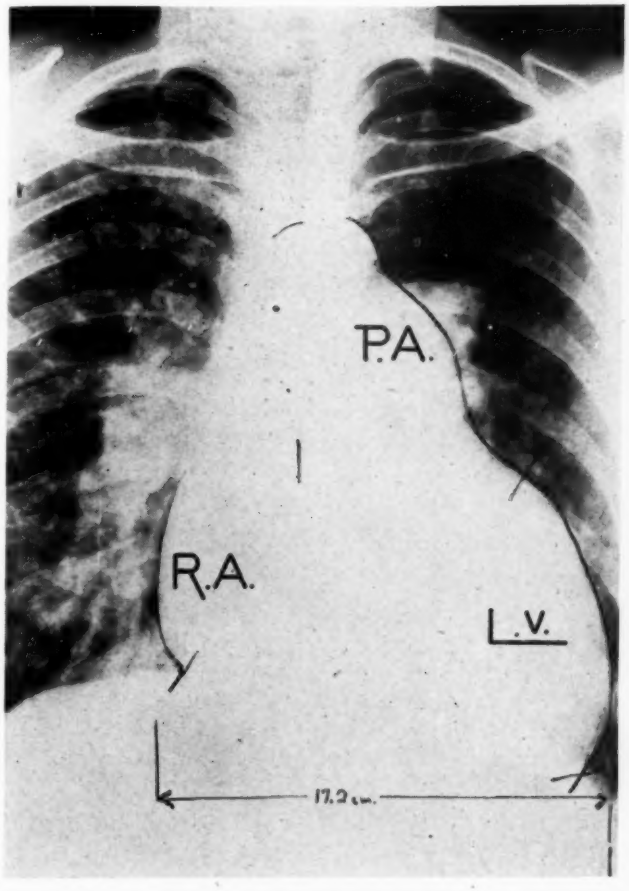

Fig. 2.—Case 1. The frontal view of the teleroentgenogram shows the markedly dilated pulmonary artery with very prominent hilar markings. *P.A.*, Pulmonary artery; *L.V.*, left ventricle; *R.A.*, right atrium.

Physical findings were quite similar on each admission and are summarized. The blood pressure was 160/45. The patient was well developed and well nourished. He was orthopneic and had pitting edema of both ankles. The carotid pulsations were accentuated and a venous pulse was noted. In the lungs, there were a few fine basal râles bilaterally. The heart was enlarged to the anterior axillary line in the sixth intercostal space. The cardiac rate was 120 per minute and was irregular. A loud to-and-fro murmur was heard at the aortic area and in the third left intercostal space at the left sternal border. At the apex was a longer and lower-pitched systolic murmur. There was no diastolic murmur heard at the apex. The liver was palpable three fingerbreadths below the right costal margin. The extremities revealed pitting ankle edema.

The electrocardiograms all showed right axis deviation. The latest electrocardiogram was taken in March, 1946. This tracing showed auricular fibrillation, right axis deviation, and digitalis effect (Figs. 1). The teleroentgenograms revealed a markedly enlarged heart with both right and left ventricular hypertrophy. The transverse diameter of the heart measured 17.2 cm., which is 43 per cent over normal according to the Hodges-Eyster[6] correlation. The pulmonary artery was considerably dilated. The lung fields showed prominent hilar shadows with marked accentuation of the vascular pattern (Fig. 2). The blood Wassermann and Kahn tests were positive.

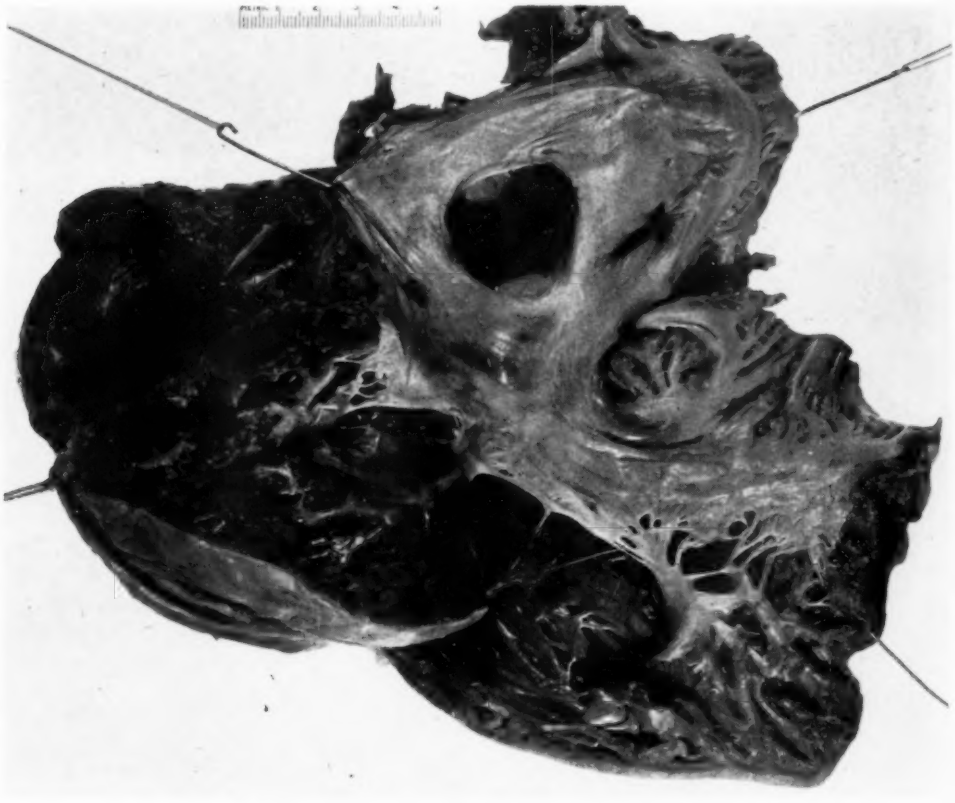

Fig. 3.—Case 1. The large interatrial septal defect is seen from the right side of the heart. Note the marked right ventricular hypertrophy.

Pathologic Findings: The post-mortem examination revealed the body of a 60-year-old Mexican man, which weighed 45.3 kilograms and measured 155 cm. in length. It was well developed and well nourished. There was pitting edema of the ankles.

The pericardium was slightly thickened and was adherent to the base of the aorta in its upper portion. The pericardial sac contained about 50 c.c. of a light amber-colored fluid. The heart was enlarged and weighed 700 grams. Both ventricular chambers were dilated. The aortic valve cusps were shrunken and deformed. The commissures of the cusps were separated and thickened. The free margins were moderately thickened and the base of the aorta was very rigid. The aortic ring measured 7.5 cm. in circumference; the valve was incompetent. The pulmonary valve ring was dilated and measured 9 centimeters. The pulmonary artery distal to the valve ring was 12 cm. in circumference. The mitral valve measured 11 cm. and the tricuspid valve

measured 15 centimeters. The ostia of both the right and left coronary arteries were markedly stenosed and admitted only the tip of the small point of the scissors and measured less than 1.0 mm. in diameter. The coronary arteries distal to the ostia, however, were quite wide and patent throughout, with only a very minimal amount of atherosclerosis. The interatrial septum contained a large defect which measured 3.5 cm. in diameter (Fig. 3). This defect appeared to be congenital in origin. The margins were smooth and the defect was located in the lower part of the septum. In the right atrium there were a few firmly adherent, small ante-mortem thrombi.

Fig. 4.—Case 1. The syphilitic aortitis is seen together with the hypertrophied left ventricle. The stenosed coronary ostia can scarcely be seen just above the deformed aortic valves.

Both atria were considerably dilated, the right more than the left. The right ventricle was also very dilated. The myocardium was hypertrophied and there was diffuse scarring present. The left ventricular wall measured 17 mm. in thickness while the stretched right ventricular wall measured from 6 to 8 millimeters. The papillary muscles of both ventricles were hypertrophied. The ascending aorta measured 9.5 cm. in circumference and showed both longitudinal and transverse wrinkling, with numerous pearly plaques. There was fairly diffuse atheromatous change in the intima (Fig. 4). The descending aorta showed a moderate amount of atherosclerosis.

Microscopic sections of the aorta were diagnostic of syphilitic aortitis. Sections taken from the margin of the interatrial septal defect showed normal cardiac muscle without evidence of any inflammatory changes. The left ventricular wall showed diffuse fibrosis. Sections from the pulmonary artery were normal.

The anatomic diagnoses were: (1) Syphilitic heart disease due to syphilitic aortitis with insufficiency; (2) congenital heart disease with interatrial septal defect; (3) left and right ventricular hypertrophy; and (4) chronic passive congestion.

CASE 2.—M. C., a 67-year-old white woman, entered the Los Angeles County Hospital on Oct. 9, 1942, with ankle edema, palpitation, and moderate dyspnea. Although these symptoms had been present for four years, they had become much worse during the past three months. Since 1938, the blood Wassermann was known to have been positive. She had two courses of arsenicals and three courses of bismuth since that time. Digitalis also had been taken sporadically in the past four years.

The physical examination revealed an elderly woman in no acute distress. The systolic blood pressure was 170; the diastolic could not be accurately determined, since the sounds were heard to zero. The neck veins were moderately distended. The heart was moderately enlarged to the left. The apex was in the fifth intercostal space lateral to the mid-clavicular line. There were no thrills palpable. The rhythm was irregular and slow. There was a Corrigan pulse and "pistol shot" sounds were elicited over the large vessels. The pulmonic second sound was louder than the aortic second sound. There was a systolic murmur at the apex transmitted to the axilla. There was a diastolic blowing murmur present in the first intercostal space to the right of the sternum. It was also heard to the left of the sternum in the third and fourth intercostal spaces. There was dullness with impaired fremitus over the right posterior chest. Numerous moist râles were heard in both lungs. The liver was palpable four fingerbreadths below the right costal margin. There was pitting edema of both lower extremities.

The electrocardiogram showed auricular fibrillation, right axis deviation, and digitalis effects (Fig. 5). The patient expired before roentgenographic studies could be made. The blood Wassermann and Kahn were positive.

Pathologic Findings: The post-mortem examination revealed the body of a well-developed, fairly well-nourished white woman 67 years of age, which weighed 56.9 kilograms and measured 156 cm. in length. The pupils were dilated and equal. There was no trauma to the head or body. There was no palpable adenopathy. Edema of the ankles was present. A midline scar below the umbilicus was present.

The pericardium was smooth and glistening. The pericardial sac contained several cubic centimeters of clear yellow fluid. The heart within the chest cavity showed a markedly dilated pulmonary artery which almost completely hid the aorta. The enlargement of the heart was due primarily to the enlargement of the right atrium and right ventricle. The heart weighed 550 grams. The aortic valve measured 8 cm. in circumference and showed thickening and shortening of the margins of the cusps with separation of the commissures. There was marked tree-barking of the aorta just above the aortic valve. The mitral valve measured 8.5 centimeters. Calcific nodules were present in the endocardium of the valve. The chordae tendineae were not shortened or thickened. The left ventricular wall measured only 13 millimeters. The right ventricle was extremely dilated and hypertrophied and the stretched wall measured 6 millimeters. Although the left atrium appeared normal, the right atrium was considerably dilated. The pulmonary artery measured 11 cm. in circumference. The pulmonary valve and the pulmonary artery and its branches were widened throughout. There were atheromatous plaques present on the intimal surface of the branches. The tricuspid valve measured 16 centimeters. The foramen ovale was closed, but just superior to it there was a large defect which measured approximately 3 by 5 centimeters. The coronary ostium of the right coronary artery was only pin-point in size but the vessel throughout its length was not narrowed. The left coronary artery was normal in its course and distribution and was patent throughout. The myocardium was firm and brown in color.

The microscopic sections of the aortic valve showed the changes of syphilitic aortitis.

The anatomic diagnoses were: (1) Syphilitic heart disease due to syphilitic aortitis with insufficiency; (2) congenital heart disease with interatrial septal defect; (3) right ventricular hypertrophy; and (4) chronic passive congestion.

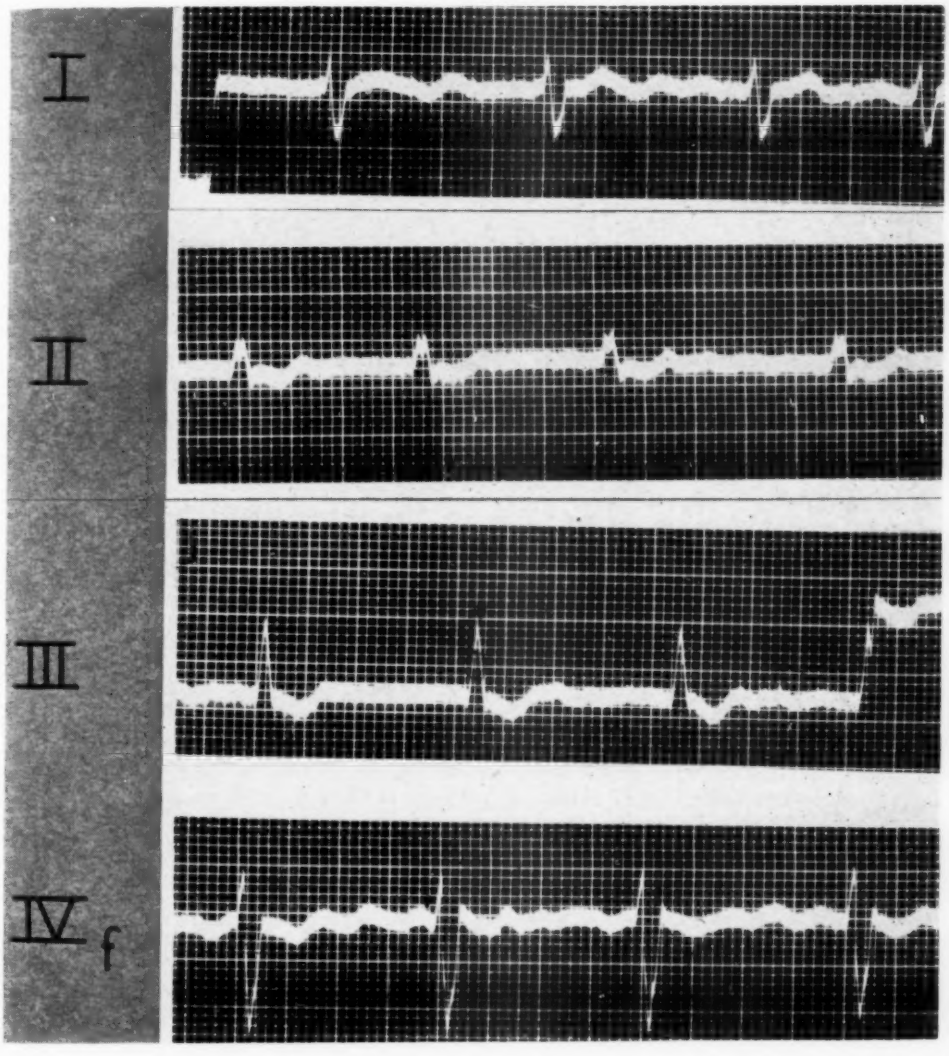

Fig. 5.—Case 2. The electrocardiogram shows right axis deviation, auricular fibrillation, and digitalis effects.

DISCUSSION

The clinical diagnosis in each of these cases was syphilitic aortic insufficiency with congestive heart failure. The clinical criteria which substantiated such a diagnosis were the usual findings of an enlarged heart, an aortic diastolic murmur, a Corrigan pulse with a very wide pulse pressure, and a history of syphilis with positive serology.

There were several inconsistent findings in both of these cases which made the given clinical diagnosis, by itself, untenable. The most apparent one was the presence of right axis deviation on all the electrocardiographic tracings in the presence of what appeared to be a free aortic regurgitation. Uncomplicated aortic insufficiency usually will cause left ventricular preponderance with left axis deviation. Auricular fibrillation is very uncommonly associated with syphilitic aortic regurgitation.[6] Auricular fibrillation was evident from the electrocardiograms in both of these cases. Extreme dilatation of the pulmonary artery, as was seen from the roentgenograms in Case 1, does not fit in with the pathologic physiology of simple aortic insufficiency. The pulmonary artery in Case 2 was also very dilated and would undoubtedly have shown up on roentgenograms had they been taken.

From the foregoing, then, one should suspect that something more was present than uncomplicated syphilitic aortic insufficiency. The answer was found by the post-mortem studies already discussed. In both patients there was a large interatrial septal defect.

The embryology of defects of the interatrial septum are well described by Patten.[8] Uhley[9] has given an anatomic as well as a physiologic explanation for the right-sided hypertrophy in hearts with an interatrial septal defect. He has presented evidence to show that the interatrial septum normally lies horizontally when the body is erect. The left atrium is superior to the right atrium in the erect position. The force of gravity, then, even in an uncomplicated interatrial septal defect, tends to cause right atrial dilatation and hypertrophy. This phenomenon is accentuated when, for any reason, the left ventricle fails.

In a heart with a simple congenital interatrial septal defect, auricular fibrillation is not unusual.

Consequently, when the clinical diagnosis is syphilitic aortic insufficiency, but the electrocardiograms show right axis deviation and possibly auricular fibrillation and the roentgenograms of the chest reveal a very dilated pulmonary artery with increased hilar shadows, consideration should be given to the diagnosis of syphilitic aortic insufficiency complicated by an interatrial septal defect.

SUMMARY

1. Two cases of syphilitic aortic insufficiency associated with a large interatrial septal defect are presented.

2. The diagnosis of such a combination of lesions may be suspected before death when the clinical syndrome of syphilitic aortic insufficiency is associated with electrocardiographic evidence of right axis deviation and possibly auricular fibrillation, with roentgenographic findings of a distinctly dilated pulmonary artery.

I am grateful to Dr. E. M. Butt, Dr. E. M. Hall, and Dr. W. P. Thompson for helpful suggestions and comment. Also, I wish to thank Mr. A. J. Lonberg and Mr. L. Matlovsky for the photography.

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Abstracts and Reviews

Selected Abstracts

Booker, W. M., French, D. M., and Molano, P. A.: Further Studies on the Acute Effects of Intra-abdominal Pressure. Am. J. Physiol. **149**:292 (May), 1947.

It has been shown that in all instances death can be produced sooner or later by maintaining an increased intra-abdominal pressure, which causes a circulatory failure produced from a venous stasis with consequent loss of plasma into the abdomen and the usual events to follow. It mattered not whether the air (used to increase the pressure) was introduced into stomach, intestine, or peritoneal cavity. A given pressure seems to cause an earlier circulatory failure and death in animals with small abdominal areas than the same pressure in animals of larger abdominal areas. Increasing the intra-abdominal pressure causes an increase in thoracic respiratory activity, most likely due to inactivity of the abdominal muscles. There is suggestive evidence that increased intra-abdominal pressure causes a damage to the myocardium which is ascribed to narrowing of the coronary arteries via the vagal pathways. The tendency of the QRS complex to return toward normal following sectioning of the vagi lends weight to this postulation.

BERNSTEIN.

Lee, R. E., and Lee, N. Z.: The Peripheral Vascular System and Its Reactions in Scurvy: An Experimental Study. Am. J. Physiol. **149**:465 (May), 1947.

In the absence of information concerning the physiology of the peripheral vascular bed in scurvy, it was decided to make direct microscopic observations on the reactions of the smallest blood vessels in living scorbutic animals. The method used involves observation with the microscope of the mesenteric capillary bed in guinea pigs which are not under general anesthesia.

The dysfunction of the peripheral vascular apparatus in scurvy, as found, displays at least two prominent features: (1) A decreased responsiveness of the contractile elements, particularly of the arterial portion beyond the pulsatile small arteries, to epinephrine, with dilatation of these muscular vessels and a relatively sluggish flow of blood; and (2) A tendency of the terminal collecting venules, which drain the capillary bed, to become dilated and engorged and to rupture with trauma.

The response of the larger vessels (more than 100 to 150 micra in diameter) to topical epinephrine tests were within normal limits. At least 85 per cent of the petechiae were located in the small collecting venules which drain the capillary bed directly. In the scorbutic animals the capillaries were of the same diameter as those of the controls, and no abnormalities of the capillary wall were observed.

BERNSTEIN.

Sosman, M. C.: Venous Catheterization of the Heart. I. Indications, Technics, and Errors. Radiology **48**:441 (May), 1947.

The author describes the technique used in the study of 100 patients by venous catheterization. There were thirteen failures in this series. These failures were attributed to venospasm which prevented proper propulsion of the catheter in two patients, to a defective catheter which did not have a proper curve and could not be properly guided in two instances; other

failures were attributed to kinking of the catheter at juction points in the venous system, to inexperience early in the series, and to lack of cooperation on the part of the patient. Ten autopsies performed on patients who succumbed to their disease or conditions unrelated to the procedure showed no trace of damage to the lining epithelium of the superior vena cava, right heart, nor pulmonary arteries.

The author used a number 9 French catheter made of radiopaque woven silk 100 to 125 cm. in length, with a single orifice at the tip. The catheter is flexible, yet sufficiently stiff that it can be twisted at its exposed end without buckling. The tip is slightly curved to facilitate its passage into the different parts of the cardiovascular system. Under aseptic precautions, following a liberal infiltration of the antecubital fossa with novcaine, an incision is made in the right or left median basilic vein. The catheter is then threaded into the vein and advanced to the desired area under fluoroscopic guidance. Spot films are taken of the various parts corresponding to the areas from which samples of blood are taken for analysis; the films are properly labelled to correspond to the blood samples. Continuous perfusion with normal saline prevents clotting of the blood in the catheter.

The comfort of the patient is important for the success of the procedure. A synthetic rubber mattress is placed on the fluoroscopic table (this does not interfere with fluoroscopy or films) and a rigid arm support is used.

ZION.

Dexter, L.: Venous Catheterization of the Heart. II. Results, Interpretations, and Value. Radiology **48**:451 (May), 1947.

The use of venous catheterization in the study of congenital heart disease offers an opportunity for the estimation of the physiologic magnitudes of the shunts of blood and the circulatory dynamics.

Venous catheterization may be helpful in the recognition of atrial septal defects in the following manner: (1) The catheter may be introduced through the defect; and (2) arterial blood may be aspirated from the right auricle. The recognition of uncomplicated ventricular septal defects depends on the finding of a significantly higher oxygen content of the blood in the right ventricle than in the right auricle. A patent ductus arteriosus is detectable by finding a higher O_2 content of the blood in the pulmonary artery than in the right ventricle. The author presents several histories of confirmed cases of each of these types of congenital lesion. Charts of the O_2 content and pressure of the right auricle, right ventricle, pulmonary artery, and capillaries are included.

Since cure or improvement of certain types of congenital heart disease is possible by surgical intervention, venous catheterization promises to be an important aid in the diagnosis.

ZION.

Freeman, N. E., and Storck, A. H.: Successful Suture of the Abdominal Aorta for Arteriovenous Fistula. Surgery **21**:623 (May), 1947.

The authors state that Pemberton and associates performed the first successful repair of an arteriovenous fistula involving the abdominal aorta, and that their case which is reported in this paper is the second one successfully operated upon. The patient was a battle casualty who suffered a bullet wound of the abdomen three inches below the ensiform cartilage, just to the right of the midline. He was paralyzed from the waist down. An emergency laparotomy revealed a large retroperitoneal hematoma. During the next two months, a pulsating epigastric mass with an intense thrill was noticed. Four months after injury an operative repair of the fistula was carried out through a right paramedian incision. Exposure of the aorta was obtained by incising the peritoneum and transversalis fascia to the left of the midline and reflecting the contents of the left side of the abdomen to the right. Bleeding from the aorta was controlled by passing rubber tubings around it just below the diaphragm and again just proximal to the inferior mesenteric artery. The left renal artery, also, was surrounded by tubing. The aorta was separated from the fistula and closed with a transverse running stitch of No. 000 Deknatel silk.

The postoperative course was complicated by a temporary anuria and azotemia and also by a transient increase in the paralytic signs of the lower extremities. At a follow-up examination eight months later the patient was free from recurrence of the fistula and the paralytic signs had cleared considerably.

LORD.

Rector, E. W.: Evaluation of the Basal Vascular Tone Test as an Indication for Sympathectomy in the Treatment of Surgical Lesions of the Major Arteries. Surgery 21:630 (May), 1947.

Naide and Säyen have described a test for the measurement of vascular tone in which the skin temperature response of the finger tips during a cooling period of fifteen minutes in a constant room temperature of 20° C. is determined. If the temperature of the finger tips is below 25° C., then the patient is considered to have high vascular tone. On the other hand if the temperature of the finger tips remains above 25°C., then the patient has low vascular tone.

By means of this test, Rector attempted to evaluate the collateral circulation of patients with a major arterial lesion of an extremity in which surgical correction of the lesion was contemplated. If the vascular tone was high, sympathectomy was employed as an adjunct measure. The results were compared with the clinical evaluation of the patient's collateral circulation and increased vascular tone, as judged by such signs as cyanosis, sweating, and constricted veins. The author concluded that the clinical evaluation of the basal vascular tone of the patients studied was more accurate than the cooling method of Naide and Säyen.

LORD

Massell, T. B.: The Fluorescent Wheal Test for Collateral Circulation in the Preoperative Evaluation of Patients With Aneurysms and Arteriovenous Fistulas. Surgery 21:636 (May), 1947.

The author has studied the collateral circulation of twenty-eight patients with arteriovenous fistulas and aneurysms by means of the Matas-Moszkowicz flushing test and the fluorescent wheal test of Neller and Schmidt. For both tests a modified Matas compressor was used. When an important collateral branch arises immediately proximal to the aneurysm, both tests may give faulty information about the collateral circulation because of compression of this vessel along with the main artery leading to the aneurysm. With this exception, both tests give useful data, although the fluorescent wheal test is somewhat more accurate, simpler, and less painful to the patient, and also gives a more accurate, reproducible end-point than the Matas-Moszkowicz test.

When the collateral circulation proved inadequate, lumbar sympathetic blocks usually produced significant improvement when the collateral circulation was tested by these two methods. If improvement was noted, lumbar sympathectomy was carried out in some patients with involvement of the popliteal artery.

LORD.

Condorelli, L.: Physiopathology of the Venous Circulation. Atti Società Italiana Cardiologia, page 5 (May 2), 1943.

Venous pressure has been studied by means of continuous kymographic tracings. The author considers the venous system as having a "free flow" and reflecting chiefly the resistance of the veins. This resistance is the result of venous tonus. Oscillations of venous pressure of from 5 to 20 mm. of water, lasting twenty to sixty seconds, were observed. Slower oscillations, lasting from five to ten minutes, also were seen. Numerous studies concerning the regulation of venous tonus and several functional tests were studied.

The author confirms the existence of venous hypertension in acute and adhesive pericarditis, and in tricuspid stenosis. A further cause of venous hypertension is congestive failure which, paradoxically, is accompanied by increase of venous tonus. Low venous pressure is common in old age, and seems to be associated with hypotonus of the veins. The speed of venous circula-

tion was studied by two successive injections of decholin, one in a vein of the hand, the other in one of the veins of the arm (or by similar injections in the veins of the lower limb). The difference between the two circulation times represents the velocity of the blood between the two points.

The hand-to-elbow time varies from 40 to 120 seconds; the foot-to-femoral time, from 32 to 100 seconds.

LUISADA.

Selvini, A.: New Studies on the Differential Theory of the Electrocardiogram. Cuore e circolaz 31:69 (May-June), 1947.

The author discusses the so-called "differential theory" of the electrocardiogram. According to this, the electrocardiogram results from the algebraic summation of two monophasic curves. In order to verify this theory, the author ran a series of animal experiments. His aim was to obtain two monophasic currents, actually caused by the heart, and to determine the result of their summation.

A first series of experiments was made with two isolated frog hearts. In each of these the currents were obtained by applying an electrode over a previously injured area of the myocardium so that each of the two hearts gave a monophasic curve. When the two hearts were connected with the two electrodes of a galvanometer, the resultant curve was that of a normal electrocardiogram. A slight asynchronism between the rates of the hearts caused first simultaneous monophasic waves of an opposite direction, then progressive summation with a normal electrocardiogram.

A second series of experiments was performed on guinea pig and dog hearts. Two unipolar leads with opposite polarity from two damaged areas (one at the base, one at the apex) of the exposed heart were connected to a galvanometer through an interposed free electrical field, represented by physiologic salt solution in a Petri dish. While the two separate unipolar leads gave monophasic waves, the summation of the two, owing to a slight asynchronism, gave a nearly normal electrocardiographic complex. Various considerations on the possible applications of this differential theory follow.

LUISADA.

Macht, D. I.: Thromboplastic Properties of Penicillin and Streptomycin. Arch. internat. de pharmacodyn. et de thérap. 74:399 (June), 1947.

An extensive investigation was undertaken by the author to ascertain the frequency and degree of the thromboplastic effects of penicillin in the blood of higher animals. Not only was the ordinary amorphus penicillin examined, but also the more recent crsytalline sodium salts of penicillin and the isolated crystalline penicillin principles. Streptomycin was also tested.

In this report over 200 experiments on blood coagulation were performed by the Lee-White method. These studies were confined to the clotting of whole blood. The majority of the experiments were made on rabbits and cats, although a few experiments were also made with dog's blood and human blood.

Amorphous penicillin of every brand examined produced marked acceleration of clotting time, whether injected intravenously or intramuscularly and even when mixed with amphojel and administered by stomach tube. The onset of this property can be noted usually within fifteen or twenty minutes after injection, but in some cases it is most marked about one hour after injection. The effect persists usually for several hours. When the newly produced sodium salt of crystalline penicillin (C.S.C.) was examined, however, the thromboplastic effect was much less striking. The author secured and examined the comparative effects on coagulation of the four crystalline penicillin principles. Penicillin G (benzyl-penicillin) and penicillin F (Pentenyl-penicillin) were much less thromboplastic in their efficiency than penicillin X (hydroxy-benzyl-penicillin) and K (heptyl-penicillin). To express this in another way, penicillin X is the most thromboplastic and is followed closely by penicillin K, while penicillin G and F are not very markedly active in this respect. It was found that a small dose of penicillin X added to penicillin G produced a synergistic effect and hastened coagulation much more than a large dose of

penicillin G alone. Streptomycin was found to be also markedly thromboplastic for blood of rabbits and cats.

The author states that amorphous penicillin produces marked acceleration in clotting time, irrespective of whether it is administered by vein or parenterally. The newer crystalline penicillin (C.S.C.) was not as thromboplastic as the amorphous preparation. He points out that when rabbits were repeatedly used for these experiments, the coagulation time of those animals was shortened for long periods of time so that for examination of new preparations fresh animals had to be employed. Also, this shortening of coagulation time in rabbits and cats could be antagonized and cancelled by suitable doses of dicoumarol administered by stomach. It is the opinion of the author that, next to the chemotherapeutic properties of penicillin and streptomycin and to their low toxicity, the most important pharmacologic finding is their thromboplastic activity.

BELLET.

Vineberg, A. M., and Jewett, B. L.: Development of an Anastomosis Between the Coronary Vessels and a Transplanted Internal Mammary Artery. Canad. M. A. J. 56:609 (June), 1947.

In 1946, one of the authors described an anastomosis between the left internal mammary artery and the left coronary circulation, which occurred in a dog ninety-nine days after transplantation of the left internal mammary artery into the wall of the left ventricle. These experiments have been continued with the basic objective of supplying a fresh source of arterial blood to the heart muscle. To do this the left internal mammary artery has been partially removed from its normal position on the chest wall and implanted into the myocardium of the left ventricle.

In a series of dogs, the internal mammary artery was tied at its distal end between two ligatures and cut. The free end was drawn through a previously prepared tunnel in the wall of the left ventricle and fixed in this position. Ten animals were killed at the end of three or four months; seventeen animals are still alive, many of which were operated upon more than a year ago.

Of the ten dogs killed, two, or 20 per cent, showed a definite communication between the left internal mammary artery and the left coronary circulation. In eight of the ten animals which were sacrificed, the transplanted internal mammary artery had revascularized the surrounding structures. In the five animals in which a constricting scar formed, the artery proximal to this area developed communications with the chest wall and intercostal vessels on the left side. In one animal, where the artery had pulled out of the heart, a communication developed between the artery and the vessels of the chest wall and the pericardium.

BELLET.

Friedman, S. M., and Friedman, C. L.: Non-Renal Hypertension. Canad. M. A. J. 56:655 (June), 1947.

The authors were particularly concerned with cases of hypertension that are without any apparent renal basis in the early stages. It seemed to them that once the concept of nonrenal essential hypertension was acceptable, the rise in blood pressure might be regarded as a compensatory phenomenon. They believe that a state of equilibrium exists between the net profusion pressure of the blood and the perfusibility of the tissues, and that an upset in this equilibrium might well demand an increase in hydrostatic pressure. Many factors are operative in the maintenance of this equilibrium. These authors were especially interested in those substances which contribute to the tissue osmotic pressure.

The testis and the vitreous humor of the eye are the major sources from which hyaluronidase has been extracted. The substrate hyaluronic acid appears to be widely distributed throughout the tissues of the body and has been related to the tissue-binding substance. The authors viewed this particular enzyme system as only one of many possible systems of that type and not necessarily the metabolic mechanism for which they were looking. The first experiment devised by the authors attempted to remove surgically the sources of hyaluronidase (mucinase) as far as possible.

Ninety male albino rats were divided into four groups: Group 1 served as untreated controls; Group 2 served as castrate controls; in Group 3, enucleation of the eye was performed at the start of the experiment; and Group 4 was composed of both castrated and eye-enucleated animals. All operations were performed on the same day. Four weeks after operation, blood pressure, renal clearance of inulin and sodium paramino hippurate (PAH), and pulse rates were determined. These tests were completed in ten days and the animals sacrificed on the fortieth day.

Renal clearance studies were carried out on ten animals from each group. The eye-enucleate animals of Group 3 failed to gain weight as well as the controls. The average blood pressure in Groups 3 and 4 was significantly elevated when compared with the controls. The weight of the testes in the animals of Group 3 was considerably below the normal, animals in this group being partially castrated by the enucleation. Moderate enlargement of the heart occurred not only in the hypertensive Groups 3 and 4, but also in the castrate controls (Group 2). Since the blood pressure was not elevated in the castrate control series (Group 2), the cardiac enlargement could not have been due to a hypertension. The clearance of both inulin and PAH was significantly elevated, both to the same degree, so that the filtration factor remained the same. There is thus a hemodynamic alteration expressed as an increase in renal blood flow. The tubular mass is likewise increased, suggesting that the kidneys are hyperfunctional.

Enucleation thus elevated the blood pressure and secondarily induced a hemodynamic and functional alteration in the kidney. A hypertension, therefore, has been produced which is neither renal nor neurogenic in origin, making it clear that the blood pressure may be raised without existing renal damage.

BELLET.

DeTakats, G., and Fowler, E. F.: The Surgical Treatment of Hypertension, the "Neurogenic" Versus Renal Hypertension From the Standpoint of Operability. Surgery 21:773 (June), 1947.

The authors point out that cases of so-called "neurogenic," that is, nonrenal hypertension traditionally have been considered suitable for sympathectomy whereas cases of hypertension due to a renal humoral mechanism have been deemed poor candidates for surgical intervention. DeTakats and Fowler challenge this concept and present detailed case reports of nineteen patients, some of whom have shown significant postoperative improvement when definite renal involvement was present but renal function reasonably good. Unilateral renal disease, renal trauma, toxemia of pregnancy, pyelonephritis, scarlatinal nephritis, and "rheumatic kidney" were the etiological bases of the renal factor in twenty-three patients with hypertension. When the functional impairment was not great, the postsympathectomy results were gratifying. On the other hand, the authors believe that neurogenic hypertension may be "a pluriglandular type of hypertension governed by the pituitary." They observed that this group fails to benefit by operative intervention on the sympathetic nervous system.

LORD.

Kebrer, H. E.: Electrocardiographic Changes Following Air Encephalograms. Deutsche med. Wchnschr. (June 6), 1947.

The author found profound changes in electrocardiograms of fifty-one patients during and following the introduction of air into the brain ventricles. There was a marked flattening of the T wave, which in some instances became negative. In addition, there was a shift of the pacemaker from the sinus node to lower auricular levels, the production of nodal rhythm, and even ventricular automatism with widening of the ventricular complexes.

The author advises that air encephalograms be undertaken with due caution in those persons whose conduction system appears to be already considerably damaged. He also concludes that low or diphasic T waves, abnormalities in the form and position of the P wave, and occasional extrasystoles at times have an extracardiac origin. The author mentions briefly the results obtained by various workers which might suggest that the midbrain is one of the extracardiac sources of origin of these ectopic rhythms.

KRAMER.

Cavelti, P. A.: Studies on the Pathogenesis of Rheumatic Fever. II: Cardiac Lesions Produced in Rats by Means of Autoantibodies. Arch. Path. 44:13 (July), 1947.

Killed streptococci in conjunction with emulsions of heart, connective tissue, and skeletal muscle can cause the development of antibodies to homologous tissues. Can these antibodies react specifically, in vivo, with respective tissue components and act as a pathologic agent? The hearts of rats thus immunized were studied from the standpoint of myocardial and valvular disease and its possible resemblance to the human lesions of rheumatic fever. Grossly, little was noted, since the smallness of the rat heart precluded detailed examination. Histologically, the chief changes occurred in the connective tissue structure of the heart; namely, the valves, valve rings, and the interstitial and perivascular tissue of the myocardium. The valvular lesions were at the free ends and in the valvular rings, and consisted of infiltrative cellular lesions, often nodular. Various cellular types were present: the monocytic series predominated; fibroblastic proliferation and relatively large basophilic cells contributed. Some of the latter were multinuclear; together with connective tissue degeneration and frequent nodular formation the combined features suggested Aschoff bodies, yet classical lesions of the latter type could not be identified with certainty. These infiltrations caused definite thickening of some valve leaflets. Similar lesions were found in the connective tissue of the myocardium. Widespread fibroblastic activity and subsequent scarring were also notable in the myocardium of many of the rats.

Lesions resembling periarteritis nodosa were seen around arterial vessels in the heart and also in other organs.

No similar cardiac lesions were seen in the hearts of rats treated with streptococci alone or connective tissue emulsion alone. Cavelti concluded that the lesions were due to the presence of autoantibodies. He further concluded that tissue emulsions from the heart and connective tissue were equally potent in the production of the cardiac lesions, tissue emulsions from skeletal muscle were the least so. Connective tissue is apparently the site of the antigen responsible for the cardiac lesions.

Cavelti formulates a hypothesis of the genesis of rheumatic fever as follows: Streptococcic substances reacting with connective tissue of the host lead to formation of autogenous antigen. This antigen incites the development of specific antibodies, which in turn precipitate the rheumatic lesions by reacting, in vivo, with the antigen situated in the tissues.

GOULEY.

Alexander, F., Gold, H., Katz, L. N., Levy, R. L., Scott, R., and White, P. D.: The Relative Value of Synthetic Quinidine, Dihydroquinidine, Commercial Quinidine, and Quinine in the Control of Cardiac Arrhythmias. J. Pharmacol. & Exper. Therap. 90:191 (July), 1947.

Using a large group of subjects with paroxysmal auricular fibrillation, auricular flutter, ventricular tachycardia, and auricular fibrillation, the authors were able to show that the action of synthetic and commercial quinidine, given in the same dosage, was similar in both degree of slowing and duration of effect. Both were equally effective in the prophylaxis of cardiac arrhythmias. Dihydroquinidine, used in half the dosage of synthetic and commercial quinidine, had a similar action. Quinine compared to synthetic and commercial quinidine and dihydroquinidine was relatively ineffective.

GODFREY.

Wilburne, M., Katz, L. N., Rodburd, S., and Surtshin, A.: The Action of N, N-Dibenzyl-Beta-Chloroethylamine (Dibenamine) in Hypertensive Dogs. J. Pharmacol. & Exper. Therap. 90:215 (July), 1947.

The authors studied the effect of intravenous injection of dibenamine in seven hypertensive (renal hypertension) dogs. Three normotensive dogs were used as controls. The animals were unanesthetized, and the pulse rate and blood pressure readings were followed over periods of from two days to several weeks.

Both the hypertensive and normotensive dogs showed the same type of reaction to intravenous dibenamine. An initial fall in blood pressure and rise in pulse rate was followed by a widely fluctuating blood pressure which persisted for as long as two days after a single dose. Prolonged administration of dibenamine over a period of three weeks produced no sustained effect upon the blood pressure of three hypertensive dogs. Dibenamine shortened or inhibited adrenalin-produced ventricular tachycardia and reduced the pressor response to adrenalin.

GODFREY.

Chen, K. K., and Anderson, R. C.: Digitalis-Like Action of Some New Glycosides and Esters of Strophanthidin. J. Pharmacol. & Exper. Therap. **90**:271 (July), 1947.

Ten new glycosides related to digitalis-like glycosides and five esters of strophanthidin were tested. The mean lethal dose was determined. In some, the action compared favorably with that of ouabain.

GODFREY.

Crystal, D. K., Edmonds, H. W., and Betzold, P. F.: Symmetrical Double Aortic Arch. West. J. Surg. **55**:389 (July), 1947.

The authors present in an 8-week-old infant a case of double, symmetrical right and left aortic arches, which embraced the trachea and esophagus tightly and which united dorsal to the esophagus to form the descending aorta.

At the age of 10 months, generalized convulsions followed some of the apneic attacks to which the child was subject. It was observed that the superficial veins of the torso and neck had become a great deal more prominent. A barium study of the esophagus showed a constant indentation of the esophagus from behind at the level of the second and third dorsal vertebrae. This was interpreted as the aortic arch passing behind the esophagus. The symptoms could then be explained on the following assumptions: (a) a persistent right aortic arch; (b) the descending aorta lying in its normal position to the left of the vertebral column; and (c) constriction of the esophagus and trachea by a left aortic arch, or by the ligamentum arteriosum, or by both the arch and the ligament.

When the patient was one year old, operation was attempted. The atresic ductus arteriosus was ligated and cut. At the time of operation, it was considered unwise to incise the pericardium any further cephelad because of its intimate connection with the trachea. Two hours postoperatively, the patient developed an attack similar to those experienced before operation, became apneic, and died.

Autopsy disclosed symmetrically placed right and left aortic arches of equal caliber tightly embracing the trachea and esophagus. From each of these arose the carotid and subclavian arteries to the respective sides. Behind the esophagus, the arches merged to form a descending aorta which extended downward in its normal position. The pericardium was attached above to the two arches. The left arch lay in the fold of pericardium which had seemed adherent to the trachea.

BELLET.

Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: The Circulatory Action of Theophylline Ethylene Diamine. Clin. Sc. **6**:125 (July 17), 1947.

The authors have made studies of right auricular pressure by means of cardiac cathererization, and of the cardiac output determined by the Fick principle in a group of normal subjects as well as patients with various forms of heart failure. The effect of theophylline ethylenediamine, 0.48 Gm. administered intravenously, on these observations was noted. Except in cases of emphysema, the administration of this drug was followed by a fall in venous pressure and a corresponding rise in cardiac output. This rise in cardiac output was greater than that which occurs when venous pressure falls following the application of cuffs, or after venesection, or the administration of digoxin, and led the authors to agree with others that this drug exerts an adrenaline-like action upon the myocardium.

WAGNER.

Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: Effects of Oxygen, Venesection and Digitalis in Chronic Heart Failure From Disease of the Lungs. Clin. Sc. 6:187 (July 17), 1947.

This paper reports observation on cardiac output and filling pressure in cases of congestive heart failure associated with emphysema and other chronic diseases of the lungs. These patients were divided into two groups: Patients in the first group had systolic blood pressures over 90 mm. Hg and had an increased cardiac output. Patients in the second group had systolic blood pressure below 90 mm. Hg; they were in a terminal state and exhibited a low cardiac output. Patients in the first group differed from patients with congestive heart failure due to hypertensive, ischemic, or valvular heart disease because they presented an increased cardiac output, and they further differed in that they showed a fall in cardiac output when a fall in venous pressure occurred. The authors state that the increased cardiac output found in this condition is compensatory, and harm may follow a fall in venous pressure produced by venesection or digoxin. The measures of greatest value are oxygen and thiouracil. The latter is given in an effort to reduce the general metabolism.

WAGNER.

Garvin, E. J.: Mesenteric Vascular Occlusion Complicating Thromboangiitis Obliterans. Am. J. Surg. 74:211 (Aug.), 1947.

The author reviews the brief literature on Buerger's disease in which vascular involvement of the abdominal vessels has been established. The diagnosis is based on four chief findings: (1) The clinical picture is not typical of the common surgical emergencies; (2) the degree of pain is out of proportion to the other clinical findings; (3) the only constant finding is deep abdominal tenderness unless peritonitis has developed, which is a late manifestation; and (4) the leucocyte count and pulse rate are elevated disproportionately to the temperature and other signs.

Garvin reports a case of a man, 33 years of age, who had suffered from Buerger's disease of the extremities for eight months, and who developed an acute occlusion of a large branch of the mesenteric vein. Operative resection of one and one-half feet of gangrenous bowel located in the proximal ileum was carried out. The patient was treated postoperatively by gastric decompression, penicillin, and parenteral fluids. In addition, he was heparinized for seven days. The postoperative course was moderately febrile, but recovery was complete by the twenty-fifth postoperative day, when he was discharged.

The author concludes that "in spite of the fact that the vessels in the resected portion of bowel did not show microscopically the ordinary vascular lesions seen in the thromboangiitis obliterans, yet in view of the present literature on this subject, we must consider the mesenteric vascular occlusion as part of the general picture of Buerger's disease."

LORD.

Cavelti, P. A.: Pathogenesis of Glomerulonephritis and Rheumatic Fever. Arch. Path. 44:119 (Aug.), 1947.

In previous work, the author demonstrated the formation of autoantibodies to kidney, heart, and connective tissue by immunizing rats and rabbits with emulsions of homologous tissues combined with killed streptococci. He showed, further, that such autoantibodies are pathogenic when they react with the corresponding tissues in situ. Such a process might explain the pathogenesis of rheumatic fever and glomerulonephritis. The author previously obtained streptococcus-tissue antigen corresponding to the hypothetical autoantigens by mixing (in vitro) the killed streptococci with tissue emulsions.

He now demonstrates that, with focal streptococcic lesions in rats, autogenous tissue antigens are developed and released into the blood stream. Their presence can be proven by means of antiserums to rat tissues produced in the rabbit. The most potent rabbit anti-rat tissue serum was anti-kidney serum, which reacted with the serums of the infected rat in high dilutions; this striking positive reaction was obtainable in maximum degree in twenty-four or thirty-six hours

after the initiation of streptococcic infection, and disappeared gradually in from eight to fourteen days. Rabbit anti-rat heart serum produced a much weaker reaction.

Although this phenomenon is similar to rheumatic fever in so far as the latter may be the expression of the formation of autoantibodies in response to streptococcic infection, there is one dissimilar feature: this experimental reaction appears quickly at the height of streptococcic infection, while rheumatic fever appears two or three weeks after the onset of the preceding streptococcic infection.

GOULEY.

Pearce, J. M., and Lange, G.: Cardiac Anoxia as the Factor Determining the Occurrence of Experimental Viral Carditis. Arch. Path. **44**:103 (Aug.), 1947.

The authors reviewed previous work dealing with the production of a viral myocarditis in rabbits secondary to subcutaneous inoculations or installations in the upper respiratory tract. They found that such myocardial lesions were remarkably increased by the simultaneous intravenous injection of acacia and also of pitressin extract. The authors feel that the only reasonable explanation for this phenomenon is the introduction of the factor of cardiac anoxia. This is produced by coronary artery constriction after pitressin, or by interference with gas interchange between hemoglobin and the tissues of the heart following acacia. If the authors' hypothesis is correct, the use of other drugs that would cause coronary constriction should cause the same aggravation of viral myocarditis as did pitressin. On the other hand, those drugs that have a detrimental action on heart muscle, without coronary constriction, should have no effect in increasing the extent of viral myocarditis.

In conformity with this reasoning, barium chloride and adrenalin were tried and found to cause a marked increase in the incidence of viral myocarditis. On the other hand, digitalis, papaverine, and nikethamide, given intravenously, produced no increase of inflammatory reaction in the hearts of untreated controls.

The myocardial lesions that developed after acacia had been injected into the venous blood stream were predominantly confined to the right side of the heart, while those following the injection of constrictors of the coronary arteries involved chiefly the left ventricle. This can be explained by the almost complete dependence of the left ventricular myocardium on the coronary arteries for its nutrition, while the right ventricular muscle is nourished by the numerous venous and venusinusoidal communications that link with the right ventricle lumen.

GOULEY.

Winbury, M. M., and Crittenden, P. J.: The Action of the Basic Amino Acids on the Heart and Intestine. J. Pharmacol. & Exper. Therap. **90**:293 (Aug.) 1947.

The authors studied the action of the basic amino acids (histidine, arginine, and lysine) on the heart and intestine, using both isolated and intact specimens. Arginine and lysine were found to depress the isolated frog heart, while histidine exerted a stimulating action.

Using the intact anesthetized cat, arginine and lysine, given intravenously in a solution buffered to pH 7.4, had a hypotensive action with a decrease in heart rate. Histidine at the same pH resulted in a slight rise in blood pressure. However, if given as a monohydrochloride at pH 4.0, histidine exhibited a hypotensive action similar to arginine and lysine.

Studies on the intestine of the rabbit in situ revealed a fundamental difference between the action of histidine hydrochloride and the two basic amino acids. All three relaxed the longitudinal muscles of the duodenum. However, histidine hydrochloride caused a spasm of the circular muscles, while lysine and arginine caused an inhibition.

GODFREY.

Maresh, G. J., and Farah, A. E.: The Influence of Rate of Administration Upon the Lethal Dose of Cardiac Glycosides. J. Pharmacol. & Exper. Therap. **90**:304 (Aug.), 1947.

Digoxin, oleandrin, and digitoxin were given intravenously to intact anesthetized cats. The more rapidly the individual glycoside was given, the higher was the lethal dose. As the rate of

administration was decreased, the lethal dose was diminished until a definite concentration was reached which could not be lowered by further decrease in rate of administration. This is termed the minimal lethal dose. Each glycoside has a characteristic rate of administration at which the minimal lethal dose is determined.

GODFREY.

Rogers, J. W., Sellers, E. A., and Gornall, A. G.: Intestinal Perfusion in the Treatment of Uremia. Science **106**:108 (Aug.), 1947.

Interest in removal of nonprotein nitrogenous constituents of blood by "artificial" means in cases of renal failure has been stimulated greatly by recent work. Kolff suggested that perfusion of a loop of bowel isolated surgically might prove superior in some respects to other methods presently used. It occurred to one of the authors (J.W.R.) that a specially designed intestinal tube with three lumina might make it possible to perfuse the intestine in situ, and so render surgical intervention or even aseptic technique unnecessary. By using a thin triple bore tube with a small balloon at the tip, the authors were able experimentally to perfuse any desired length of intestine without resorting to surgery on the bowel. In the dog, however, it is necessary to manupilate the tube into position through an abdominal incision. This would be unnecessary in the human.

In experiments to date, the blood nonprotein nitrogen of nephrectomized dogs has been reduced consistently and materially. For example, a lowering of the azotemia from 198 to 126, 198 to 112, and 231 to 145 mg. per 100 ml. of blood was observed in successve trials, using 12 to 18 liters of perfusion fluid over a period of about six hours. The rinsing fluid after perfusion contained 4.3 to 5.4 Gm. of nonprotein nitrogen.

A more detailed experimental study of the method is now in progress and an investigation of its clinical application is being undertaken by the authors.

BELLET.

Foisie, P. S.: Traumatic Arterial Vasospasm. New England J. Med. **237**:295 (Aug. 28), 1947.

The author discusses the findings observed in a group of patients suffering from the persistence of a relatively low-grade arterial spasm in the extremities as a complication of local injury. He points out that this type of response holds little or no threat to the viability of the limb, but, nevertheless, it is likely to cause nutritional changes which may adversely affect the functional result. No relationship exists between the severity of the original wound and the degree of arterial spasm subsequently noted. In fact, some of the most stubborn cases of vasospasm may complicate mild injuries. It would appear that the smaller, quickly closed wounds are associated with more vasospasm than are the larger, wide open ones. The production of tension in the tissues may, therefore, be a factor in the initiation and propagation of this reaction. The incidence of vasospasm is not dependent on the location of the injury nor on the structures involved.

The clinical picture of the existence of vasospasm consists primarily of color changes, involving a combination of spotty pallor and diffuse cyanosis. Dependency and exposure to a cold environment increase the cyanosis, while elevation of the extremity has a similar effect on the pallor. The cutaneous temperature of the affected limb is definitely lower than that of the normal side, and generally there is a moderate edema. The severe excruciating pain generally noted in causalgia is absent, but the patient complains of numbness, coldness, tingling, or other types of paresthesia. There is marked tenderness, out of proportion to the force of palpation, and the extremity is held immobile with the joints flexed in an attempt to minimize the pain. The most reliable sign of arterial spasm is the finding of diminished or absent peripheral pulses which are definitely altered by vasodilating procedures.

With regard to therapy, it appears necessary to maintain the extremity in a fairly warm environment and to utilize the various vasodilating procedures. Of the latter, repeated paravertebral sympathetic blocks cause transient but definite improvement. Sympathetic ganglionectomy will in some instances produce permanent relief of symptoms.

ABRAMSON.

Starr, I.: On the Later Development of Heart Disease in Apparently Healthy Persons With Abnormal Ballistocardiograms. Eight- to Ten-Year After-Histories of 90 Persons Over 40 Years of Age. Am. J. M. Sc. 214:233 (Sept.), 1947.

Ballistocardiograms were first taken in 1936. When the method was satisfactorily established, work on normal standards was begun. Normal subjects were selected from a group that would permit a follow-up over a period of years. Ten years have elapsed since the first record of this series was taken, eight years since the last. Among the ninety supposedly healthy persons in this group, ranging from 40 years to 85 years of age, four subjects had ballistocardiograms abnormal in form. Three of the four developed coronary heart disease in the years which followed. In the other eighty-six subjects the ballistocardiograms were normal in form. In these the results were arranged according to the size of the ballistocardiogram as related to actual and ideal weight. The six cases giving the smallest records in proportion to actual weight developed coronary heart disease. It was found that a line could be drawn through the data at a level 44 per cent below the average of healthy young adults referred to ideal weight, and that 50 per cent of those who fell below this line developed serious heart disease in contrast to 5 per cent of those above, a highly significant difference. Five subjects who gave ballistocardiograms normal in form and amplitude during the years 1937-39 died within the next eight to ten years. None of them developed clinical evidence of heart disease, and in two the heart was normal at necropsy. Post-mortem examinations were not done in the other three. One patient in the group with normal ballistocardiograms is of especial interest. This man, aged 79 years when originally studied, had a record which was above those of most others in his age group and equal to that of many young adults. This man is now well and active at the age of 87 years.

It is concluded from these studies that a ballistocardiogram which is abnormal in form or of unusually small amplitude is of serious prognostic significance. The ballistocardiographic method gives promise of identifying coronary heart disease far earlier in its course than has been possible hitherto.

DURANT.

White, P. D. August, S., and Michie, C. R.:, Hydrothorax in Congestive Heart Failure. Am. J. M. Sc. 214:243 (Sept.), 1947.

The authors have analyzed 100 cases of congestive heart failure showing hydrothorax at autopsy at the Massachusetts General Hospital. Fifteen cases showed unilateral right hydrothorax; thirteen, unilateral left hydrothorax. Each of the latter revealed an important factor in addition to the congestive failure, there being complete obliteration of the right pleural cavity in twelve and unilateral left pulmonary infarction in the remaining case, in contrast to only four such explanations among the fifteen cases of unilateral right hydrothorax. The remaining seventy-two cases showed bilateral pleural effusions, equal in thirty-one but predominantly right-sided in thirty-two of the remaining forty-one. The etiological type of heart disease and the side of preponderant initial ventricular strain made little difference as to the location of the hydrothorax, but the great majority of these cases at autopsy had right heart failure usually superimposed on left.

An additional 100 cases of acute left ventricular failure in hypertension or aortic valve disease were analyzed as to the subsequent occurrence of hydrothorax during the next few weeks; seventy-six showed none, while sixteen developed bilateral hydrothorax, six unilateral right, and only two unilateral left hydrothorax; of the twenty-four cases who developed hydrothorax, only six failed to show any recognized sign of right heart failure and it is possible that the venous pressure might, if recorded, have been elevated in those six cases also. Pulmonary infarction (superimposed upon, or precipitating, or aggravating the congestive failure) was found in thirty cases and played a secondary role in the localization of the hydrothorax.

DURANT.

Massee, J. C.: Atrial Septal Defect. Correlation of Autopsy Findings With Data Obtained by Right Heart Catheterization. Am. J. M. Sc. 214:248 (Sept.), 1947.

Of 1,500 patients studied by the method of heart catheterization, only one patient with atrial septal defect has come to autopsy. The literature has revealed no other case report of congenital

cardiac defect which had both heart catheter studies and autopsy. The case reported was that of a man 37 years of age, who had been diagnosed clinically as having congenital heart disease with myocardial failure and compensatory polycythemia. The right heart catheterizations revealed that: (1) the oxygen content of the right atrial blood was distinctly higher than the superior vena caval blood; (2) the oxygen content of the right atrial and right ventricular blood was the same; (3) the right ventricular (pulmonary artery) pressure was extremely high (140 mm. Hg); (4) the pressure in the right atrium was elevated; (5) calculated left ventricular output was roughly normal, right ventricular output was at least twice this. These data could only have been obtained by heart catheterization, and they helped to clarify the diagnosis of atrial septal defect and made possible the diagnosis of pulmonary vascular hypertension. After these studies, the course of the patient's condition was gradually downhill over a period of eight months. Death occurred after a series of pulmonary infarcts.

The autopsy showed a defect in the lower portion of the interatrial septum which was 5 cm. in diameter. There was marked dilatation and hypertrophy of the heart, predominantly right-sided. Bilaterally, thrombosis of many branches of the pulmonary artery, with multiple pulmonary infarcts, was found.

In discussing the correlation of the autopsy findings with the catheterization studies, it is pointed out that right atrial blood oxygen saturation can exceed the vena caval saturation in only two conditions: interatrial septal defect and aberrant pulmonary veins emptying into the right atrium, the latter condition being rarer than the former and not associated with as much cardiac enlargement. The finding of a right ventricular output roughly twice that of the left ventricle, despite the fact that the right atrial pressure was necessarily less than the left, is at variance with Starling's law. The discovery of increased right ventricular pressure, together with the fact that increased saturation of arterial blood could be obtained with oxygen inhalation, showed the presence of pulmonary vascular obstruction.

DURANT.

Fitts, W. T., Jr., and Wells, E. J., Jr.: A Case of Fatal Arterial Occlusions Due to Aneurysm of the Abdominal Aorta. Am. J. M. Sc. **214**:252 (Sept.), 1947.

A rare complication of aortic abdominal aneurysm is reported. A 66-year-old tabetic was admitted to the hospital for scrotal gangrene, developed signs of an abdominal catastrophe, and died a few hours after admission. Autopsy showed a saccular aneurysm of the lower abdominal aorta. A thrombus in the inferior mesenteric artery had produced gangrene of the large bowel, while embolic occlusions of the hypogastric arteries were evidently responsible for the scrotal and perineal gangrene. A search of the literature failed to reveal a similar case.

DURANT.

Shapiro, E., Lipkis, M. L., and Kahn, J.: "Trophic" Ulcers of the Hands Complicating Myocardial Infarction. Am. J. M. Sc. **214**:288 (Sept.), 1947.

Certain maladies of the shoulder joint, subdeltoid bursa, palmar fascia, and finger joints are recognized as sequelae of myocardial infarction. "Trophic" ulceration of the hands, however, is a rare and apparently hitherto unreported complication. The patient, a man aged 49 years, had had angina since the age of 41 years. About twelve hours after the onset of the symptoms of acute posterior myocardial infarction, two vesicles, symmetrically placed over the metacarpophalangeal joints of the index fingers, were noted. The thin coverings of these blisters ruptured spontaneously the next day and deeply punched out, painless ulcers were left, the right being twice as large as the left. There were no neurologic signs, no thickening of the palmar fascia, no arthritis of the hands, and no evidence of bursitis of the "shoulder syndrome." The pain of the myocardial infarction and of the preceding angina had been entirely limited to the chest, there being no arm radiation whatsoever. The authors believe that the promptly appearing vesicular and, later, ulcerated skin lesions in this case may be explained by antidromic stimulation of prodigious degree from the infarcted heart, and they suggest that antidromic impulses may be the mechanism of production of the other maladies of the shoulder and hand following myocardial infarction.

DURANT.

Geever, E. F.: Pulmonary Vascular Lesions in Silicosis and Related Pathologic Changes. Am. J. M. Sc. **214**:292 (Sept.), 1947.

The effect of silicosis on the pulmonary circulatory system and, indirectly, on the right heart constitutes one of the important complications of this disease. Such sequelae as pulmonary hypertension and right-sided cardiac dilatation, hypertrophy, and failure are generally attributed to obliterative vascular changes. However, with one exception, detailed descriptions of the vascular lesions and their pathogenesis are not available in the modern literature.

The author has studied the pulmonary vascular lesions and related pathologic changes in forty-three cases of silicosis, cases with complicating pulmonary tuberculosis being largely excluded. A similar series of forty-three nonsilicotic patients in the same age group was used as a control. Two morphologic processes seemed to evoke vascular changes: direct encroachment on the vascular wall by nodules or nodular masses, and infiltration of the vascular wall by dust and pigment-bearing granulation tissue. In discrete nodular silicosis the vascular lesions were not striking, as a rule, and were found only in small arteries, small veins, arterioles, venules, and capillaries. In massive conglomerate nodular silicosis the vascular lesions were severe, were found in vessels of all sizes, and were demonstrable best in sections stained for elastic fibers. Fibroblastic proliferation was an early reaction in all layers of the arterial wall; later, proliferation of vasal and capillary channels and degeneration of muscle and elastic tissue occurred. Occlusion and disruption of the vascular wall by infiltrating granulation tissue which streamed through all the layers were end results. Thrombosis of large arteries was observed in two cases of discrete nodular and seven cases of massive conglomerate nodular silicosis. The veins revealed similar occlusive and disruptive changes, but appeared to offer less resistance than the arteries. Lymphatic vessels often showed distention, stasis, and endothelial pigmentation. In massive conglomerate nodular silicosis, veins and lymphatics were often destroyed without trace.

Related pathologic changes in the heart included right ventricular hypertrophy to a thickness of 0.5 cm. or more in ten out of the twenty cases in the discrete nodular group, and in sixteen out of twenty-three cases in the massive conglomerate nodular group. Although seven patients in the former group had evidence of cardiac disability which was of major importance as a cause of death, only one instance was found in which the right-sided cardiac changes alone were responsible. Thirteen of twenty-three patients in the latter group had evidence of a major cardiac disability. In ten hearts of this group, right ventricular hypertrophy and varying degrees of dilatation were the only significant changes. Related pathologic changes in the pulmonary parenchyma (namely, fibrosis, ischemic necrosis, and ischemic cavitation) were described. Ischemic cavitation was found in the fibrous masses of seven patients in the conglomerate nodular group. Pseudocavitation due to emphysema was sometimes encountered.

Intravascular pressure changes were believed to be important factors in the pathogenesis of the vascular lesions in these silicotic patients. Increased pulmonary intra-arterial pressure due to elimination of large portions of the pulmonary vascular bed plus interference with distensibility of the remaining channels, surrounded or fixed as they are at various points by fibrous masses, would be expected to be combined deleterious factors in this respect. Anoxemia due to interference with vasal circulation was believed to result from the marked perivascular fibrous changes in massive conglomerate nodular silicosis. Adventitial vasal hyperemia and proliferation probably represented a reaction to interference with vasal circulation and an attempt to establish collateral channels.

DURANT.

Wilens, S. L.: Resorption of Arterial Atheromatous Deposits in Wasting Disease. Am. J. Path. **23**:793 (Sept.), 1947.

At necropsy, severe atheromatosis is at least twice as common in obese as in undernourished persons who are 35 years of age or older. This relationship is independent of sex, hypertension, and diabetes. The author believes that atheromatosis in man, as well as in rabbits, may be reversible, and bases this opinion on studies of autopsy material with special reference to the appearance of the aorta and coronary arteries of patients whose nutrition was known to have been

seriously impaired during their final illness. He correlated data as to the state of nutrition during health, the duration of the final illness, and the loss of weight during that time. Only patients between 40 and 60 years were included.

The evaluation of the state of nutrition at autopsy was based on the amount of adipose tissue deposited in the various body sites. The degree of atherosclerosis was graded by the extent of atheromatous deposit in the intima. The relationship of terminal weight loss and nutrition and the severity of atherosclerosis in the coronary arteries and in the aorta was striking. Twelve of twenty-four obese patients, but only two of thirty-nine poorly nourished patients, had severe atherosclerosis of the coronary arteries. If hypertensive patients are excluded, this difference is still apparent. Of the twelve obese patients, six were hypertensive, while both of the poorly nourished patients with severe atherosclerosis were hypertensive. The aorta is apparently as good a site as the coronary arteries by which to judge the relationship of nutrition and atheromatosis.

GOULEY.

Jorpes, J. E.: The Origin and the Physiology of Heparin; the Specific Therapy in Thrombosis. Ann. Int. Med. 27:361 (Sept.), 1947.

The composition of heparin is essentially that of a sulfonic ester of a high molecular polysaccharide. Its anticoagulant action is apparently related to the strong negative electric charge of the compound. The neutralization of the anticoagulant property of heparin is effected by protamine presumably because of the positive charge carried by protamine. A significant but unexplained finding is the stronger anticoagulant property of dog heparin, as compared with ox, pig, and sheep heparin, in spite of the fact that they all have the same content of ester sulfuric acid. In spite of its high degree of ionization in solution, heparin exerts very little osmotic pressure and, therefore, will not cause shrinkage of red blood cells either in vivo or in vitro.

The mast cells of Erlich, which are in close proximity to all capillaries in the body, constitute the site of formation of heparin. These cells supposedly extrude their contents into the peripheral tissue juices or almost directly into the blood stream. The liberation of the heparin in physiologic amounts from this hormonal system of mast cells maintains the proper equilibrium in so far as coagulation of the blood is concerned.

The results obtained with heparin by various writers, as well as by the author, in the treatment of thrombosis of the leg veins and of the pulmonary artery are analyzed. All these assembled data, which are based on a large experience over a number of years, indicate that the incidence of fatal embolism and disabling aftereffects of venous thrombosis have been dramatically reduced. The average dose recommended is 400 mg. divided over a twenty-four hour period. During such treatment, blood clotting determinations are not made except in elderly patients with impaired renal function.

Since heparin is highly active and nontoxic, its prophylactic use is recommended after operations or childbirth where there have been single or recurrent attacks of thrombosis in the history of the patient.

WENDKOS.

Allen, E. V., Hines, E. A., Jr., Kvale, W. F., and Barker, N. W.: The Use of Dicumarol as an Anticoagulant: Experience in 2,307 Cases. Ann. Int. Med. 27:371 (Sept.), 1947.

This paper summarizes the results obtained, over a six-year period, in (1) the treatment of venous thrombosis, arterial embolism and thrombosis, and pulmonary embolism with dicumarol or heparin combined with dicumarol in a total of 988 cases; (2) the prevention, with dicumarol, of pulmonary embolism or venous thrombosis, post partum or postoperatively, in a total of 1,238 cases; and (3) the treatment with dicumarol of myocardial infarction in a total of fifty cases.

The authors recommend that dicumarol should be used whenever an anticoagulant effect is needed over a period of days, weeks, months, or years, provided that there are available reliable determinations of the value for prothrombin in the blood. However, when both a rapid and a

prolonged effect of an anticoagulant are desired, heparin and dicumarol should be administered simultaneously. It is recommended that dicumarol be used cautiously or not at all in renal insufficiency, after operations on the brain or spinal cord, in blood dyscrasias, in ulcerative lesions of the gastrointestinal tract, and in nutritional deficiency or hepatic diseases associated with potential or actual prothrombin deficiency. The use of anticoagulants is not advised in subacute bacterial endocarditis since the danger of hemorrhage is relatively great. The dosage of dicumarol is discussed and it is concluded that the amount required will depend on the prothrombin percentage. In the author's experience, this should be maintained between 10 and 30 per cent. In the 1,983 postoperative cases, minor hemorrhage (epistaxis, hematuria, and localized ecchymosis) occurred in 3.4 per cent, while serious bleeding (from operative wounds or from the gastrointestinal tract) occurred in 1.8 per cent of the cases. Death from such serious hemorrhage occurred only twice. Serious bleeding was found to be easily controllable by repeated administration of vitamin K and transfusions of fresh blood. The post-partum state was not considered a contraindication to the use of dicumarol in the treatment of venous thrombosis or pulmonary embolism which occurred following delivery. It is the author's opinion that the introduction of dicumarol has eliminated the need for surgical ligation of veins in order to prevent pulmonary embolism.

Fatal pulmonary embolism was prevented and arterial thrombosis was halted in most instances. In addition, early treatment of sudden arterial occlusion with anticoagulants has resulted in survival of the extremity in 90 per cent of instances of embolism and 80 per cent of instances of thrombosis. An overall consideration of 1,513 postoperative patients treated with anticoagulants indicated that eighty-five patients survived who would have been expected to die from pulmonary embolism, and 250 patients were spared venous thrombosis or nonfatal pulmonary embolism. In 506 additional postoperative cases in which dicumarol was used prophylactically, venous thrombosis occurred in but two instances; there was no pulmonary embolism. The results in the fifty cases of acute myocardial infarction indicated that there was a substantial reduction in the incidence of further myocardial infarction and of arterial embolism and venous thrombosis.

WENDKOS.

Perera, G. A., and Blood, D. W.: Pressor Activity of Desoxycorticosterone Acetate in Normotensive and Hypertensive Subjects. Ann. Int. Med. **27**:401 (Sept.), 1947.

Desoxycorticosterone acetate was administered to ten normotensive subjects and fourteen patients with uncomplicated hypertensive vascular disease in doses of 5 mg. subcutaneously twice daily for one week. No significant change of the resting blood pressure appeared in the normotensive group, whereas definite increases in systolic and diastolic readings were observed in the hypertensive patients. The prompt rise in blood pressure of patients with hypertension could not be ascribed to changes in salt or water retention alone, as there were comparable changes in the normotensive group.

WENDKOS.

David, P., McPeak, E. M., Vivas-Salas, E., and White, P. D.: Dissecting Aneurysm of the Aorta: Review of 17 Autopsied Cases of Acute Dissecting Aneurysm of the Aorta Encountered at the Massachusetts General Hospital From 1937 to 1946 Inclusive, Eight of Which Were Correctly Diagnosed Ante Mortem. Ann. Int. Med. **27**:405 (Sept.), 1947.

During the ten years from 1937 to 1946, seventeen cases of acute dissecting aneurysm, proven by necropsy, were encountered at the Massachusetts General Hospital. Of these, twelve were men and five women. The men ranged in age from 47 to 69 years, and the women from 57 to 78 years. A correct ante-mortem diagnosis was made in eight instances. Associated hypertension existed in every case, but in two instances syphilitic heart disease was also present. A basal diastolic murmur developed during the acute dissection of the aorta in the majority of the cases, and was, therefore, considered an important diagnostic sign. Since electrocardiographic changes characteristic of acute myocardial infarction were lacking in this series, this finding is

suggested as an important means for differentiating the pain of acute coronary occlusion from that of acute dissecting aneurysm. Tears in the aortic intima, classified as initial, were located in the upper aorta in nineteen instances. Sixteen presented evidence of being recent, the other three appeared to be well healed and communicated with dissected endothelialized aneurysmal sacs. Eleven of the nineteen initial intimal tears were located within the first 3 cm. of the ascending aorta, six in the ascending aorta beyond the 3 cm. level, one in the arch, and the remaining example in the thoracic aorta. It was more difficult to identify the site of the rupture of the adventitia, through which blood escaped from the sac into the surrounding tissues or serous cavities. Rerupture of the dissecting aneurysmal sac into the original lumen was discovered in six instances, in two of which the secondary tear had occurred in the abdominal portion of the aorta and in the other four in one of the iliac arteries. Considering involvement of the main branches of the aorta in the dissecting process in order of frequency, the iliac arteries were affected in eight cases, the great vessels of the arch in six, the renal arteries in six, the celiac axis in five, the mesenteric arteries in five, and the coronary arteries in three cases. An arteriosclerotic involvement of some part of the aorta was described in every case. Medionecrosis, which is now recognized as being by far the main etiological factor of dissection of the aorta, was found in thirteen cases; it was not typical in two cases and was absent in the other two cases. Nine patients died within twenty-four hours and six within one to six days following the onset of the aortic dissection. A healed dissecting aneurysm which had developed previously, was noted at necropsy in three of the cases. The immediate cause of death was acute dissection of the aorta in only two cases, whereas in the remainder, it was hemorrhage into the pericardial sac with resultant cardiac tamponade.

WENDKOS.

Mellinkoff, S. M., and Higgins, J. R.: The Heart Rate in Malaria; a Review of 90 Cases. Ann. Int. Med. **27**:433 (Sept.), 1947.

The authors studied the heart rate during bouts of pyrexia in ninety cases of malaria, confirmed by the identification of the parasite in thin or thick blood smears. Of these, eighty-five were examples of infection with Plasmodium vivax, two with Plasmodium falciparum, and three with Plasmodium malariae. The results of the study indicated that one-fourth of the patients had a relative bradycardia, which, however, was never less than 70 per minute.

WENDKOS.

Solarz, S. D.: So-called "Infarction Type" Electrocardiographic Changes Following Paroxysmal Tachycardia. Ann. Int. Med. **27**:447 (Sept.), 1947.

The author describes a case of a 40-year-old aviator whose electrocardiograms for a two-week period following cessation of an attack of paroxysmal tachycardia showed varying degrees of abnormality in the form of the T waves in the conventional limb and CF leads. No explanation for the T wave changes is offered, but the author discards the possibility that myocardial infarction or quinidine effects were responsible.

WENDKOS.

Gordon, I.: Mechanism of Lipophage Deposition in Atherosclerosis. Arch. Path. **44**:247 (Sept.), 1947.

The author reviewed and commented on the present knowledge and theories concerning the pathogenesis of atherosclerosis. He believes that Leary's work is the final link in a chain of evidence that began many years ago with the development of alimentary hypercholesteremia in rabbits. After cholesterol ingestion by these animals, the cells of the reticuloendothelial system take up the esterified cholesterol and then become detached, entering the blood stream and infiltrating the intima of the aorta.

Gordon objects to the term "chemotaxis" as an explanation of this infiltrating process, but emphasizes the old physiologic concept of a heavy central cellular concentration with a clear peripheral zone in the circulating column of blood. The endothelial cells filled with cholesterol,

known as lipophages, being lighter than the other blood cells, drift into the clear peripheral zone of the blood column and under the influence of the blood pressure are forced into the intimal structure of the aorta. Localized dilatations of the blood vessel increase this tendency for lighter cells to fall away from the rapidly moving column on to the sides of the vessel. A third factor that would promote this slowing up and drifting process would be eddying of the blood stream.

The physicochemical properties of the lipid-laden lipophages allows for the formation of what might be called a pseudopod, which, first becoming adherent to the intimal surface, becomes the means for the wedging in and entrance of the body of the cell into the intimal structure.

The entrance of the lipophage into the intima is the earliest sign of aortic atheromatosis. Both Leary and Gordon believe that this lipid material is intracellular from the beginning. The infiltration of these lipid-laden cells beyond the intima finds the first barrier at the internal elastic lamella. Gordon points out that medial infiltration is further impeded by the fact that beyond the internal elastic lamella there is a concentric series of probably sixty-five sheaths of elastic tissue which, together with smooth muscle, constitute the medial structure. The aortic intima, therefore, becomes the depository for the most part of whatever cholesterol-laden cells leave the blood stream. The reason that the aorta is the site of atheromatosis far more than any other blood vessel is that the blood pressure in the aorta is greater than in any other part of the arterial system.

The author does not believe that the capillary blood vessels found in the intima of atheromatous aortas are a causative factor of the atheroma.

He points out in summary that the rabbit feeding experiments with cholesterol bear an authentic relationship to atheromatosis in man inasmuch as all significant human atherosclerosis is associated with hypercholesteremia and an increased number of the circulating lipophages.

GOULEY.

Winder, C. V., and Thomas, R. W.: Cardiovascular and Respiratory Effects of the Anti-Histamine Agent B-Dimethylaminoethyl Benzhydryl Ethel Hydrochloride (Benadryl Hydrochloride). J. Pharmacol. & Exper. Therap. **91**:1 (Sept.), 1947.

In the intact dog anesthetized with phenobarbital, benadryl hydrochloride injected intravenously typically elicited a short vascular depression followed by a slight prolonged rise in arterial pressure. This action was not influenced by vagal section or by isolation of the carotid and aortic bodies.

The action of benadryl hydrochloride on the isolated rabbit heart suggests that its action is an intrinsic one upon the myocardium. It causes a variable slight depression in contractions and a fleeting increase in coronary blood flow followed by a more lasting decrease. Respiratory changes, increased rate and decreased depth of respiration, were abolished by vagotomy and carotid denervation.

GODFREY.

Gold, H., Modell, W., Cattell, M., Osenton, J. G., and Cotlove, E. W.: Action of Digitalis Glycosides on the Central Nervous System With Special Reference to the Convulsant Action of Red Squill. J. Pharmacol. & Exper. Therap. **91**:15 (Sept.), 1947.

Purified derivatives of red squill, when given to the rat by vein, intramuscularly, or orally, produce a picture which is characteristic. There is an initial brief "shock-like" period (usually only seen with intravenous administration) followed by a period of two to ten hours when the animal appears perfectly normal. Then there is the onset of progressive muscular weakness alternating with periods of violent strychninelike convulsions. The animal dies because of respiratory paralysis during the convulsions. During all of the time following the administration of the drug, the pulse is strong and regular, the heart continues beating after cessation of respiration, and there is no evidence of ventricular fibrillation or other toxic digitalis-like effects on the heart.

The problem that this chain of events presents is whether the convulsant action of red squill is a property of its cardiac glycosides or is due to the action of other impurities. The rat is known to be highly resistant to the cardiac action of the digitalis glycosides in general. Other

digitalis glycosides (digitoxin, gitalin, folerin, ouabain) produce convulsions in a manner similar to red squill in the rat. The convulsant action appears more highly developed in some glycosides than in others. Convulsions have been observed in species other than the rat (cat and frog) with digitalis glycosides. Derivitives of red squill act like typical digitalis glycosides in the frog, cat, and man. Given intravenously to rats, very large doses of red squill will cause death shortly after its administration. The cause of death is cardiac, the effects resembling those of digitalis poisoning in other species. The convulsant action of red squill, therefore, is due to a peculiarity of both the drug and the species of animal it has been most extensively used in. Many digitalis glycosides have convulsant properties; however, the amount of drug necessary to produce convulsions far exceed the toxic cardiac dose in most species of animals.

GODFREY.

Wollenberger, A.: Metabolic Action of the Cardiac Glycosides. I. Influence on Respiration of Heart Muscle and Brain Cortex. J. Pharmacol. & Exper. Therap. **91**:39 (Sept.), 1947.

Using slices of guinea pig heart muscle in the presence of glucose or lactate, ouabain, in moderate dosage, was found to produce an increase in oxygen consumption. In high dosage ouabain caused a decreased oxygen consumption. Brain slices (guinea pig) respond similarly, but are one and one-fifth times as sensitive as cardiac muscle. Homogenized brain or heart preparations do not respond to ouabain in moderate dosage with an increased oxygen consumption, nor would intact specimens respond unless an appropriate substitute (such as glucose) was present. If brain slices that had been exposed to ouabain and were actively respiring were washed and placed in a fresh solution, they showed a cessation of respiration.

It is inferred from these findings that ouabain probably works upon the cell surface, increasing permeability to the exogenous substitute; subsequently, the increased permeability causes a loss of some respiratory catalysts.

GODFREY.

York, C. L., and Fischer, W. J. H., Jr.: Plasma Volume Determinations in Rheumatic Subjects During Oral Salicylate Therapy. New England J. Med. **237**:477 (Sept. 25), 1947.

Seven rheumatic patients were given sodium salicylate orally in dosages sufficient to maintain salicylate blood levels of 35 mg. per 100 cubic centimeters. A plasma volume increase of from 4 per cent to 38 per cent was observed in five of these patients. It was considered probable that this rise was the result of increased sodium ion in the presence of impaired cardiac function. Hematocrit and plasma protein concentration did not consistently reflect the changes in plasma volume. A definite and persistent depression of prothrombin activity usually occurred. Serious hemorrhage occurred in one patient.

KAY.

Fishberg, A. M.: Simulation of Myocardial Infarction by Esophageal Tear. J. Mt. Sinai Hosp. **14**:296 (Sept.-Oct.), 1947.

The author describes two instances of tear of the esophagus in which the diagnosis of myocardial infarction was considered.

Case 1 is that of a 39-year-old man in whom esophagoscopy disclosed two small lesions about 34 and 35 cm. from the incisor teeth, which were regarded as fibrolipomas. After an evening of drinking he retched and vomited twice, felt agonizing substernal pain, and was given a hypodermic of one-quarter grain of morphine sulfate, followed by three similar injections during the day, with little relief. Oxygen by mask did not help. The initial diagnosis was myocardial infarction. However, two electrocardiograms were negative. Esophagoscopy performed twelve days after admission revealed a transverse tear of the esophagus at a level of 37 centimeters. Exploration of the mediastinum four days later showed enormous dilatation of the lower esophagus, but disclosed no evidence of any extraesophageal lesion. Jejunostomy was performed. After this the patient improved rapidly.

Case 2 is that of a 40-year-old man who was seized with violent pain localized in the upper abdomen and lower anterior chest after a protracted drinking bout during which he vomited repeatedly. The pain became localized in the substernal region and the patient seemed to be going into shock. Myocardial infarction was considered as the likely diagnosis. Later, subcutaneous emphysema appeared in the neck and the chest, which suggested that rupture of the esophagus was probably the diagnosis. The patient sank rapidly. Necropsy showed the posterior surface of the esophagus to be lying in a bed of brownish necrotic material. Section of the esophagus showed a laceration one inch long just above the cardiac portion of the stomach. A second laceration parallel to the first and one-half inch long was also present.

BELLET.

Oppenheimer, B. S., and Zacharias, L.: A Note on the Effect of a Vitamin K-Like Quinone Upon Experimental Renal Hypertension in Dogs. J. Mt. Sinai Hosp. **14**:542 (Sept.-Oct.), 1947.

The authors investigated the effect of the water-soluble vitamin K, synkayvite, on five dogs rendered hypertensive by the application of the Goldblatt clamp to the renal arteries. No significant effect in reducing the high blood pressure of these dogs could be observed during or after the administration of this water-soluble vitamin K. The dosage employed in dogs was as follows: 10 mg. for the first two days, 20 mg. for the next six days, and 38 mg. for the next seven days, making a total of 406 mg. injected intramuscularly in fifteen days.

BELLET.

Freis, E. D., and Smithwick, R. H.: The Effect of Lumbodorsal Splanchnicectomy on the Blood Volume and "Thiocyanate Space" of Patients With Essential Hypertension. Am. J. M. Sc. **214**:363 (Oct.), 1947.

This investigation was undertaken as a part of a comprehensive study of the effects of sympathectomy on the hemodynamic functions of patients with essential hypertension. It was considered worth while to rule out the possibility that the reduction in blood pressure is accompanied by significant alterations of total blood volume, and, incidentally, to obtain information on the effects of the operation on the intravascular and extracellular fluid compartments of the body.

Repeated blood and "available fluid" ("thiocyanate space") determinations were made on a series of ten cases for periods up to six months following lumbodorsal splanchnicectomy. The total blood volume was reduced in nine cases in the period from eight days to two weeks following operation, due primarily to a diminution in red cell volume. Despite a continued reduction of blood pressure, the total volume was restored to the approximate preoperative level at the end of six months following operation. A slight reduction of the hematocrit value persisted, the deficiency being made up by a compensatory increase in plasma volume. Coincident with the reduction in blood volume noted in the second postoperative week, there was an increase in "available fluid" volume. This elevated value was restored to the preoperative level over a period of several months. Previous observations that the total blood volume is within normal limits in patients with essential hypertension were confirmed. In relation to surface area, the "available fluid" volume of hypertensive subjects was also found to be within the normal range. The reduction in blood pressure following sympathectomy is not dependent upon changes in total blood or "available fluid volume."

DURANT.

Kramer, D. W., and Abramson, E. B.: Flourescein Studies in Peripheral Vascular Disorders. Am. J. M. Sc. **214**:368 (Oct.), 1937.

Eighty-nine patients were studied with fluorescein (4 c.c. of a 20 per cent solution rapidly injected into the antecubital vein) for the appearance time at the lips, hands, and feet. Sixty-five of this series had some form of vascular disease; twenty-four cases presumably had no vascular disease. Various ages and both sexes were represented in the study. The appearance time

in the lips in the nonvascular group was 14.4 seconds and 16 seconds for the patients with vascular disorders. The arm-to-hand time showed an average of 28.5 seconds for the nonvascular cases and 31.2 seconds for the vascular group. The arm-to-foot time ranged from 30 seconds to 3 minutes. However, most of the cases showed an appearance time within 60 seconds; the average for the nonvascular group was 53.4 seconds, with 61.4 seconds for the vascular cases. When the appearance time was beyond 60 seconds, the vascular series predominated over the nonvascular by about 2.5 to 1. Other features which may explain delayed appearance time are old age and cardiac disease. The appearance time is not so easily recognized in the lower extremities and in the Negro. The following figures are suggested for the normal appearance times: arm-to-lip, 12 to 16 seconds; arm-to-hand, 18 to 28 seconds; arm-to-foot, 26 to 60 seconds (average, 53.4). The fluorescein test is superior to those tests which use substances requiring subjective sensations for the end point. The end point with this method is readily recognized. Fluorescein is nontoxic and is readily excreted by the kidneys. Despite the unavailability of a more definite normal standard for arm-to-foot time, the authors were impressed with the delay in appearance time in the lower extremities among patients with known vascular disorders. From this they infer that it gives information relative to the status of the peripheral circulation. It is helpful in deciding and selecting the proper type of ulcer for grafting. It may be of assistance in determining the level for amputation, although the authors have had no personal experience in this respect.

DURANT.

Ferrer, M. I., and Sokoloff, L.: The Antidiuretic Effect of Morphine and Demerol in Congestive Heart Failure. Am. J. M. Sc. **214**:372 (Oct.), 1947.

The influence of morphine on mercurial diuresis was studied in nine patients with congestive heart failure. In three, morphine produced an antidiuretic effect. In two patients, demerol also showed an antidiuretic effect. The total chloride excretion during mercurial diuresis was reduced by both drugs. It is suggested that this antidiuretic effect, while probably not operative in all patients, cardiacs or otherwise, is of sufficient importance in some cases of cardiac decompensation to account for certain poor results with mercurial diuretics.

DURANT.

Wachstein, M.: Glycogen Storage (Von Gierke's) Disease Predominantly Involving the Heart. Report of a Case With Histochemical Phosphatase Studies. Am. J. M. Sc. **214**:401 (Oct.), 1947.

The eighteenth proven case of von Gierke's disease with marked enlargement of the heart is described. On microscopic examination glycogen storage was demonstrable in the cells of various organs, including the brain, the nerve cells in the mesenteric plexus of the intestinal tract, and the Küpffer cells of the liver. The involvement of the Küpffer cells in this case and in the report of Wolff contradicts the conclusion that, in contrast to Gaucher's and Niemann-Pick's disease, the reticuloendothelial system in von Gierke's disease is not ever involved in the abnormal cell metabolism. In the kidneys, no regular distribution within the tubular segments is seen with glycogen disease, whereas in diabetes mellitus, glycogen is found in the terminal segment of the proximal convoluted tubules and to a lesser degree in the ascending limbs of Henle's loop. The histochemical distribution of alkaline and acid phosphatase in the liver, kidney, adrenal, and heart of the author's case was found to be normal, in contrast to previous reports to the contrary. Marked hyperplasia of the Langerhans' islands in the pancreas with preponderance of beta cells was present. It is suggested that this might be due to the increased demand for insulin, related to the abnormally high and persistent rise in blood sugar provoked by the ingestion of carbohydrates in many patients with von Gierke's disease.

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THE III INTER-AMERICAN CARDIOLOGICAL CONGRESS, CHICAGO, JUNE 13-17

The Inter-American Society of Cardiology has authorized the meeting of the III Inter-American Cardiological Congress to be held in Chicago, June 13 to 17, 1948, at the Michael Reese Hospital and at the Stevens Hotel. The Congress is under the auspices of the Society and the National Heart Associations of the Western Hemisphere.

This meeting will take place immediately before the American Heart Association annual meeting, June 18 and 19, and the American Medical Association meeting, the week of June 20. Delegates are chosen by the National Heart Associations. Active members in the United States include physicians approved by the American Heart Association.

Physicians wishing to participate in the Congress may obtain an application blank and full information from the Office of the III Inter-American Cardiological Congress, at the Michael Reese Hospital, Chicago. A registration fee of $15 will be charged. This amount must accompany the application blank, payable to Dr. Richard Langendorf, Secretary-Treasurer of the Congress. Registration must be made not later than April 1.

Each member attending the Congress will be permitted to read in full no more than one paper. This paper must be based on unpublished material. Abstracts, limited to 200 words, must reach the offices of the III Inter-American Cardiological Congress, not later than April 1, 1948.

Additional papers may be submitted to be read by title. If the number of papers exceeds the number which can be accommodated, the President of the Congress will select those to be read in full. The reading time for each paper will be fifteen minutes, including illustrations, with five additional minutes for discussion. However, papers to be presented at the plenary sessions, to be selected by the President of the Congress, will be limited to twenty minutes, with ten minutes for discussion.

Papers submitted will not be published by the Congress. The proceedings and abstracts of communications of the Congress will be published in a special number of the American Heart Journal. Papers presented at the Congress may be published elsewhere by the authors after the Congress has adjourned. All English abstracts will be translated into Spanish. The Congress office has requested authors to submit their abstracts not only in the original language, but also in the officially authorized translation.

The opening session of the Congress will take place on Sunday afternoon, June 13, at two o'clock, in the Grand Ballroom of the Stevens Hotel. This session will be limited to official addresses of welcome and greetings. Plenary sessions will take place in the North Ballroom of the Stevens Hotel on Monday morning, June 14, and Thursday afternoon, June 17. Ordinary sessions will take place in the Michael Reese Hospital. Two simultaneous meetings will be held in the Rothschild Auditorium and the Sarah Morris Amphitheater. All morning meetings will be held from 9 to 12 o'clock and all afternoon meetings from 2 to 5 o'clock.

A business meeting will be held in the Rothschild Auditorium, Michael Reese Hospital, at 8 o'clock, Thursday evening, June 17.

Hotel and travelling arrangements must be made by members personally. The American Express Company is the official agent for the Congress. Two hundred rooms have been reserved for members of the Congress.

The American Heart Association invites all members of The Congress to attend its Annual meeting, June 18 and 19. The official delegates will be guests at the annual banquet of the American Heart Association.

Chairman of the Honorary Council of the Congress is Dr. James B. Herrick, Chicago, and the Council's United States members include Dr. Henry A. Christian, Boston; Dr. George Dock, Pasadena; Dr. Rudolph Matas, New Orleans; Dr. Paul D. White, Boston; Dr. Carl J. Wiggers, Cleveland; Dr. Frank N. Wilson, Ann Arbor, Michigan.

Officers of the Congress are: Dr. Louis N. Katz, President; Dr. Richard Langendorf, Secretary-Treasurer; and Mrs. Marie Cole de Pardo, Executive Secretary. Vice-presidents from the United States include Dr. Arlie R. Barnes, Rochester, Minn., President of the American Heart Association; Dr. George K. Fenn, President of the Chicago Heart Association; and Dr. Harry A. Durkin, President of the Illinois Heart Association.

The Founder and Permanent Honorary President of the Inter-American Society of Cardiology is Dr. Ignacio Chavez of Mexico City. The Executive President is Dr. Teofilo Ortiz Ramirez of Mexico City. Members of the Board of Directors from the United States include Dr. Barnes, Dr. George R. Herrmann, Galveston, Texas, Dr. William J. Kerr, San Francisco, and Dr. Howard B. Sprague, Boston.

The United States member of the International Council of Cardiology is Dr. Paul D. White, Boston.

NATIONAL HEART WEEK

The greatly enlarged National Heart Week Campaign (February 8-14) of the American Heart Association, which appealed directly to the public for funds for the first time, was reflected in the increased amount of press and radio publicity given to this observance. Possibly the greatest proportional increase in the amount of publicity cooperation was registered in the field of radio. Several popular network programs devoted themselves to extended promotions for the fight against heart diseases.

"Truth or Consequences," which is conducted by Ralph Edwards and sponsored by Proctor and Gamble, and which is heard over the National Broadcasting Company network on Saturday nights, 8:30 to 9:00 P.M., E. S. T., made the American Heart Association the beneficiary of public contributions in its "Walking Man" contest which was continued over a period of many weeks. Paul Whiteman scheduled a "Memory Tune Contest," beginning March 1 on his Monday through Friday record broadcasts over the American Broadcasting Company network at 3:30 P.M., E. S. T., to solicit contributions for the American Council on Rheumatic Fever of the American Heart Association.

Other notable features in the radio phase of the National Heart Week campaign included a broadcast appeal by Hollywood screen actress Ingrid Bergman. Officials of the American Heart Association who broadcast special messages during National Heart Week included Dr. A. R. Barnes, President, who shared a program with Dr. Thomas Parran, Surgeon General of the United States; Dr. H. M. Marvin, Executive Secretary, who was interviewed by Clifton Fadiman; and Dr. Charles A. R. Connor, Medical Director. Federal Security Administrator Oscar Ewing also broadcast a special Heart Week appeal.

Many news and women's commentators devoted time on their broadcasts to appeals for public support in the fight against heart disease, and many commercial network programs included special spot announcements in their regular broadcasts. Magazine articles concerning heart disease appeared preceding, during, and after National Heart Week in such magazines as *This Week*, *Saturday Evening Post*, *Woman's Home Companion*, *American Magazine*, *American Home*, *Newsweek*, *Time*, *Forbes Magazine*, *Look*, *Parent's Magazine*, *The Woman*, *American Mercury*, *Cosmopolitan*, *Pathfinder*, *Hygeia*, and *Science Illustrated*. In addition, magazines published by cooperating trade associations and other organizations published articles and editorials on heart disease. Publications in which these appeared included the *American Legion Magazine*, *The Rotarian*, *The Lion*, and the *American Druggist*.

One of the biggest achievements in the magazine field for the heart disease campaign was the precedent-breaking lead editorial in the January 31 issue of the *Saturday Evening Post* in which the editors for the first time made a specific appeal for funds for the campaign, listing the address to which these funds should be sent. An editorial appeal also appeared in *Collier's*.

Newspaper coverage for National Heart Week was thorough and widespread as a result of the enthusiastic response from feature writers, columnists, syndicates, press associations, and picture services who were acquainted with the facts about heart disease several months before the campaign began.